UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

JOHN RUFFINO and MARTHA RUFFINO, Husband and Wife,	)	
Plaintiffs,	)	**Civil Action No.: 3:17-cv-00725**
v.	)	**Jury Demand**
DR. CLARK ARCHER and HCA HEALTH SERVICES OF TENNESSEE, INC. d/b/a STONECREST MEDICAL CENTER,	)	**Judge Crenshaw** **Magistrate Judge Newbern**
Defendants.	)	

AFFIDAVIT OF DR. TROY POPE

The affiant, Troy Pope, M.D., states under oath as follows:

1. I am over the age of 18, and I am competent to testify regarding the matters in this affidavit.

2. I was licensed to practice medicine in Kentucky and practiced medicine, including the specialty of Emergency Medicine, in Kentucky, during the 12 month period immediately prior to February 17, 2016.

3. A copy of my CV is attached to this affidavit.

4. I have reviewed materials and records in this case that include (1) Bates numbered medical records from StoneCrest Medical Center for the February 17, 2016 ER presentation and care, (2) Bates numbered medical records from Centennial Medical Center for February 2016, (3) the imaging performed at StoneCrest and Centennial in February 2016, and (4) the deposition

testimony given by (a) Dr. Clark Archer, (b) Nurse Carol McCulloch, (c) Nurse Robert Bromley, (d) John Ruffino, and (e) Martha Ruffino.

5. I earned my undergraduate degree from the University of Virginia in 1998. I earned my medical degree from the Medical College of Georgia School of Medicine in 2002. My post-graduate training in medicine included completing a residency program in Emergency Medicine at the University of Kentucky in 2005. I have been certified by the American Board of Emergency Medicine since 2006.

6. I have practiced the medical specialty of Emergency Medicine for over 10 years, and this includes seeing and treating stroke patients in an ER setting, and working with nurses in an ER setting, including during the provision of care and treatment to stroke patients. This experience also includes seeing how treatment for stroke patients in an ER setting can improve patient outcomes based on during what time interval after the onset of signs and symptoms since the time that the patient was last seen neurologically normal appropriate treatment is provided for such a stroke.

7. Since 2013, I have continuously worked as an ER physician at St. Joseph London Hospital in London, Kentucky.

8. Based on my education, training, and experience, I am familiar with the recognized standard of acceptable professional practice that applied to the care and treatment provided to John Ruffino on February 17, 2016 in the StoneCrest ER in the Smyrna, Rutherford County, Tennessee medical community or in similar medical communities (the standard of care). In February 2016, one medical community I was familiar with that was similar to the Smyrna, Rutherford County, Tennessee medical community is Laurel County, Kentucky. This familiarity includes the performance of initial assessments by nurses, ongoing monitoring by nurses, neurological checks

(neuro checks) by nurses, physical examinations by ER physicians, and actions and decision-making by ER physicians – including the ordering of imaging, initiating tPA, transfer to comprehensive stroke centers, and working with and communicating with a consulting neurologist regarding these treatment components, all of which are affected by the patient's signs and symptoms of a new stroke, the onset of those signs and symptoms, when the patient was last neurologically normal prior to the time / care in question, and recent medical literature regarding outcomes for stroke patients as published in peer-reviewed medical journals.

9. As a result of applying my education, training, and experience to my review of the case materials referenced above, I have formed opinions regarding (1) what care and treatment was required under the standard of care as it applied to the care and treatment provided to John Ruffino on February 17, 2016 in the StoneCrest ER in the Smyrna, Rutherford County, Tennessee medical community or in similar medical communities and (2) whether the care that was provided fell below what was required under that standard of care. Also based on my education, training, and experience, I am familiar with the likely outcomes for stroke patients, including based on factors such as the patient's signs and symptoms of a new stroke, the onset of those signs and symptoms, when the patient was last neurologically normal prior to the time / care in question, and the recent medical literature regarding outcomes for stroke patients as published in peer-reviewed medical journals, and I have formed opinions in this matter on (3) causation.

10. A key determination in an ER setting for a stroke patient with regard to what care and treatment is required to be provided is when the patient was last seen neurologically normal. It is important for treating health care providers to be aware of a patient's condition with regard to whether and when they are neurologically normal, to communicate any such information to other providers when there is a belief that a patient has signs or symptoms of stroke, and for the ER

physician in such a patient's care to promptly and properly act based on that information. When a patient was last seen neurologically normal is important with regard to stroke treatment because that information affects what type of treatment should be provided, because certain treatment is likely to have a positive effect on a stroke patient's immediate and long-term outcome if that treatment is provided promptly enough that irreversible brain injury has not already occurred due to the lack of proper blood flow caused by that stroke. For Mr. Ruffino, the medical records from StoneCrest and the deposition testimony of Nurse Carol McCulloch and Nurse Tony Bromley indicate that the medical providers involved with Mr. Ruffino's care from the time he presented to the ER at approximately 0949 through at least 1200 observed and recognized that Mr. Ruffino was neurologically normal. By the time that Dr. Archer first saw the patient at approximately 1220, the last time that the patient was seen neurologically normal was 1200 that same day.

11. When Dr. Archer saw the patient at approximately 1220 and identified neurological deficits, including abnormal speech and right-sided facial weakness, these were new neurological problems compared to what is documented in the medical records and what Nurse McCulloch and Nurse Bromley testified was the patient's condition from 0949-1200 that same day. When Dr. Archer saw the patient at approximately 1220, this was less than one hour after the patient was last seen neurologically normal at 1200, and Nurse Bromley testified that he told Dr. Archer by 1300 that day that the patient had been neurologically normal from 1000-1200 that day.

12. When Dr. Archer identified these new neurological deficits at or soon after 1220, these changes were present less than one hour after the patient was last seen neurologically normal by a healthcare provider at 1200. Dr. Archer was required under the standard of care to initiate the administration of tPA and arrange for transfer to a comprehensive stroke center for additional treatment, which likely would have included an endovascular thrombectomy.

13. Even if there were stroke symptoms present at approximately 0800-0830 on February 17, 2016, when Dr. Archer first saw the patient and recognized neurological deficits Dr. Archer was required under the standard of care to initiate the administration of tPA and arrange for transfer to a comprehensive stroke center for additional treatment, which likely would have included an endovascular thrombectomy.

14. Dr. Archer is the health care provider who communicated with the consulting neurologist, Dr. Chitturi, on the afternoon of February 17, 2016 regarding Mr. Ruffino. Nurse Bromley testified that ER nurses at StoneCrest did not communicate with consulting neurologists, and that this was the practice in the StoneCrest ER. It appears that Dr. Chitturi was not aware that the nurses who had cared for the patient from 0949-1200 on February 17, 2016 observed and recognized that the patient was neurologically normal during that period of time, and as Nurse Bromley testified Nurse Bromley told Dr. Archer by 1300 that day. Dr. Archer and Nurse Bromley were required by the standard of care to effectively communicate the fact that Mr. Ruffino was neurologically normal from 1000-1200, including during the serial neuro checks done during that time by the same nurse – Nurse Bromley. To the extent that Dr. Chitturi was not aware at the time that he was involved in the patient's care on February 17, 2016 that the medical providers involved with Mr. Ruffino's care from the time he presented to the ER at approximately 0949 through at least 1200 observed and recognized that Mr. Ruffino was neurologically normal, including during the performance of neuro checks at 1000, 1015, 1030, 1045, 1100, and 1200, Dr. Archer and Nurse Bromley fell below the standard of care by not effectively communicating that significant information in a way that would get to Dr. Chitturi that the patient was neurologically normal as late as 1200 on February 17, 2016, in that this information would likely have affected the care and treatment that Dr. Chitturi recommended and helped arrange.

15. When Dr. Archer identified these new neurological deficits at or soon after 1220, these changes were present less than one hour after the patient was last seen neurologically normal by a healthcare provider at 1200. Had Dr. Archer taken action to make sure that the patient was provided with treatment for this new stroke soon after 1220, the patient likely would have had a better outcome – including that the patient would have less of a deficit and less severe ongoing problems from the stroke. The treatment that could have been provided by Dr. Archer and/or under his direction and/or management was to administer IV tPA and to arrange for transfer to a comprehensive stroke center. Had those things been done within at least 6 hours of Dr. Archer first seeing the patient at approximately 1220, Mr. Ruffino would have had a better outcome from his stroke. Dr. Archer did not do this– either directly or via arranging for other physicians to provide the necessary care. Dr. Archer did not provide any such care, did not arrange for any other physician to provide any such care, and instead Dr. Archer claims that it was too late by the time that Dr. Archer saw the patient for the type of treatment mentioned herein to likely improve the patient's outcome.

16. To the extent that any physician or other person claims that the stroke that occurred on February 17, 2016 occurred by 0800 or 0830 that day, I respectfully disagree. Any neurological symptoms that Mr. Ruffino had by 0830 that day were, at most, caused by a TIA (transient ischemic attack), which is different than a stroke, and it was not until at or after 1200 that day that Mr. Ruffino had the first sign or symptom of the severe stroke that he suffered that day. The TIA or TIAs occurred that morning, but the stroke did not manifest until after 1200 that day, and for the purposes of treating that stroke, Mr. Ruffino was last seen neurologically normal at 1200 that day. However, even if there were stroke symptoms present at approximately 0800-0830 on February 17, 2016, when Dr. Archer first saw the patient and recognized neurological deficits it

was still within 6 hours of 0800-0830 for proper treatment to have likely provided a better outcome from the stroke. The treatment that could have been provided by Dr. Archer and/or under his direction and/or management was to administer IV tPA and to arrange for transfer to a comprehensive stroke center. Had those things been done within at least 6 hours of Dr. Archer first seeing the patient at approximately 1220, Mr. Ruffino would have had a better outcome from his stroke. In other words, if there were stroke symptoms present at approximately 0800-0830 on February 17, 2016 that anyone thought were persistent and continuous through when Dr. Archer first saw the patient and recognized neurological deficits by 1220-1300, it was still within 6 hours of 0800-0830 for proper treatment to have likely provided a better outcome for this stroke patient.

17. To the extent that any physician claims that whether the stroke occurred in the M1 or M2 segment in the brain affects the issue of whether timely treatment from the time Dr. Archer identified neurological deficits are or around 1220, I respectfully disagree. Regardless of what segment of the vascularization of the brain the occlusion was in that was causing the stroke that afternoon, my opinion remains that had the treatment referenced herein been provided within at least 6 hours of Dr. Archer first seeing the patient at approximately 1220, Mr. Ruffino would have had a better outcome from his stroke. This is because Mr. Ruffino likely had not suffered significant, irreversible brain injury by 1220, and therefore there were real benefits that proper and timely treatment could have provided in response to Mr. Ruffino's stroke had that treatment been started within the 6 hour time window within which Mr. Ruffino was last seen neurologically normal for stroke purposes, at 1200, and when Dr. Archer first saw neurological changed by 1300. These benefits provided via timely treatment for the stroke with tPA and an endovascular thrombectomy would be due to that treatment helping to improve blood flow through the blood vessel that was not receiving proper blood flow. Medical literature published in peer-reviewed

journals that demonstrate the beneficial effect that such treatment can have on stroke patients is attached to this affidavit as Collective Exhibit 2.

18. All of my opinions included in this affidavit are opinions that I hold to a reasonable degree of medical probability, or said otherwise, to a "more likely than not" standard. The facts from the documents I have reviewed, as listed above, that are part of the basis for my opinions include, in addition to the facts referenced above, the following:

On February 17, 2016, Mr. Ruffino presented to the ER at StoneCrest at 0949 (StoneCrest 1). He called his boss while he was driving for work and he reported feeling dizzy (StoneCrest 11). His boss called 911, and Mr. Ruffino pulled his car over (StoneCrest 11).

The initial symptom onset was at 0830 that same day was documented as sudden in onset, and he arrived at the ER by ambulance at 0948 and was triaged by 0956 (StoneCrest 3, 10 and 11). He was triaged within 90 minutes of the initial symptom onset.

Mr. Ruffino had been on Neurontin for four days for "spells" that had been occurring for a month (StoneCrest 13).

The nurse who did the initial ER assessment was **Carol McCulloch, RN** (StoneCrest 11). Nurse McCulloch had approximately 30 years of ER experience by this time (Deposition of Nurse McCulloch, at 27:18-21).

Nurse McCulloch performed the initial assessment of Mr. Ruffino in the StoneCrest ER on February 17, 2016, and her first contact with him was at 0958 (Deposition of Nurse McCulloch, at 11:7-12:23).

If Nurse McCulloch thought an ER patient was having a stroke or recently had the acute onset of a new stroke, she could call a Code Stroke or make sure that a physician or other provider

was aware of the situation, but she did neither such thing (Deposition of Nurse McCulloch, at 7:13-8:9 and 28:19-21).

Nurse McCulloch did not observe a single neurological deficit in Mr. Ruffino when she performed the initial assessment in the ER (Deposition of Nurse McCulloch, at 28:23-29:9).

Based on her experience in the ER and with stroke patients by February 2016, Nurse McCulloch does not have "any reason" to think that Mr. Ruffino was having a stroke at the time of her initial assessment and she missed it (Deposition of Nurse McCulloch, at 30:20-25).

Mr. Ruffino did not have any neurological complaints during the initial ER assessment (Deposition of Nurse McCulloch, at 19:6-10).

When Nurse McCulloch performed the initial assessment of Mr. Ruffino in the ER, everything was completely normal, including he was alert and he could move all his extremities (Deposition of Nurse McCulloch, at 22:6-10 and 23:1-12).

Nurse McCulloch classified him as CTAS 3/urgent, which is "right in the middle" of the 1-5 range (Deposition of Nurse McCulloch, at 23:13-24:13; StoneCrest 11). If Nurse McCulloch felt that Mr. Ruffino was in the midst of a new stroke, she would not have classified him as a 3 (Deposition of Nurse McCulloch, at 25:8-18). Nurse McCulloch classified Mr. Ruffino as a 3 during her initial assessment of him in the ER on February 17, 2016 because she did not think he was having a stroke at that time (Deposition of Nurse McCulloch, at 25:19-26:23).

When **Robert Bromley, RN** saw Mr. Ruffino at 1000 as the nurse who would care for him, and then documented later about this initial contact, Nurse Bromley knew that the "Onset of Current Episode" was "Less Than 1 Hour Ago" (StoneCrest 11). Nurse Bromley testified that this entry means that the onset of whatever was present at 1000 first occurred within one hour of 1000 (Deposition of Nurse Bromley, at 54:20-55:5).

Nurse Bromley was familiar with what the standard of care required of him in caring for ER patients in February 2016 (Deposition of Nurse Bromley, at 22:1-5). By February 2016, Nurse Bromley had been an RN since 2007 (Deposition of Nurse Bromley, at 5:12-16). By February 2016, he had worked in the StoneCrest ER for 5-6 years (Deposition of Nurse Bromley, at 6:22-7-6 and 73:10-12). He usually worked at least two days a week in the StoneCrest ER (Deposition of Nurse Bromley, at 8:10-15). Nurse Bromley does not have any notes or documentation that is not contained in the StoneCrest chart (Deposition of Nurse Bromley, at 11:8-14).

Nurse Bromley has observed ER patients with stroke-like symptoms (Deposition of Nurse Bromley, at 15:6-8). In February 2016, he was familiar with the type of signs and symptoms that could exist that might indicate a patient was in the midst of a new stroke – including facial droop, weakness, or slurred speech (Deposition of Nurse Bromley, at 15:18-16:8).

In February 2016, Nurse Bromley knew how to do a thorough and complete neuro check (Deposition of Nurse Bromley, at 94:10-14).

At (1) 1000, (2) 1015, (3) 1030, (4) 1045, (5) 1110, and (6) 1200, Nurse Bromley documented that the neuro checks he performed at those times demonstrated that the patient was completely neurologically normal (StoneCrest 15-17). Nurse Bromley testified that he did neuro checks at those times and that his documentation regarding those neuro check is accurate (Deposition of Nurse Bromley, at 80:4-7 and 104:1-9).

Nurse Bromley remembers Mr. Ruffino as an ER patient (Deposition of Nurse Bromley, at 11:15-20).

At 1000, Nurse Bromley performed a neuro check and he recognized that every neurological item that was a part of his neuro check was normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 55:19-56:5, 74:15-22, 83:15-19, 86:10-14;

StoneCrest 12 and 15).[1] At 1000, Nurse Bromley recognized that Mr. Ruffino did not have slurred speech, he was moving his arms, he was moving his legs, he walked to the bathroom, and he changed his own clothes (Deposition of Nurse Bromley, at 77:17-78:8). Nurse Bromley believes that the neuro check he performed on Mr. Ruffino at 1000 was performed per the applicable standard of care (Deposition of Nurse Bromley, at 82:1-6).

Nurse Bromley testified that he had no reason to think at 1000 that this patient had a single sign or symptom of a stroke (Deposition of Nurse Bromley, at 90:16-19). If he thought Mr. Ruffino began to demonstrate any signs or symptoms of a stroke (of which a physician was not aware) he would have told a physician so that a Code Stroke could be called (Deposition of Nurse Bromley, at 90:20-91:1).

At 1001, a Troponin I was ordered (StoneCrest 34). At 1002, a PTINR was ordered (StoneCrest 34). Mr. Ruffino's PT was 10.1 [9/5-11/6] and his INR was 0.95 [0.9-1.1] (StoneCrest 6).

At 1002, a head CT was ordered and it showed no acute intracranial abnormality, but there was calcific plaque of the distal left vertebral artery (StoneCrest 7, 36, and 63). This head CT did not demonstrate any tissue changes suggesting a new onset stroke or consistent with a prior stroke.

At 1008, Nurse Bromley recognized that the patient did not have an acute stroke or neurological diagnosis, as he documented in his corresponding note (Deposition of Nurse Bromley, at 56:11-57:17; StoneCrest 12). Nurse Bromley agreed that his documentation indicates that the patient was "completely normal" at 1008 with regard to neurological signs, symptoms, and conditions (Deposition of Nurse Bromley, at 58:12-17; StoneCrest 12). Around this time, the

[1] Nurse Bromley testified that the only mention in his documentation regarding dizziness refers to that reported dizziness being going on for a month (Deposition of Nurse Bromley, at 68:6-69:22; StoneCrest 12). Nurse Bromley testified that if he ever wanted to document that he thought Mr. Ruffino had dizziness under his care, he could have typed that into a note, and he never typed in such a thing (Deposition of Nurse Bromley, at 130:14-131:1).

patient passed the swallow screen, which led to Nurse Bromley providing the patient with food to eat (Deposition of Nurse Bromley, at 124:4-20).

At 1015, Nurse Bromley performed a neuro check, every neurological item that was a part of his neuro check was completely normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 64:10-15 and 92:4-8; StoneCrest 15-16).

At 1015, a PCXR was performed that was interpreted as being normal (StoneCrest 64).

At 1030, Nurse Bromley performed a neuro check, every neurological item that was a part of his neuro check was completely normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 92:11-21; StoneCrest 12). At 1030, and as Nurse Bromley documented, Mr. Ruffino walked to the restroom with a steady and even gait (Deposition of Nurse Bromley, at 93:3-25; StoneCrest 15-16).

At 1045, Nurse Bromley performed a neuro check, every neurological item that was a part of his neuro check was completely normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 94:16-20; StoneCrest 16).

At 1100, Nurse Bromley performed a neuro check, every neurological item that was a part of his neuro check was completely normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 95:1-12; StoneCrest 17).

At 1200, Nurse Bromley performed a neuro check, every neurological item that was a part of his neuro check was completely normal, and his corresponding note documents this (Deposition of Nurse Bromley, at 95:14-24; StoneCrest 17).

Nurse Bromley testified that Mr. Ruffino was "completely neurologically normal" at 1200 on February 17, 2016, which he knew as a result of his ongoing neuro checks under his watch (Deposition of Nurse Bromley, at 98:12-21).

At 1207, an EKG was performed that was abnormal, with the specific findings including sinus bradycardia, possible left atrial enlargement, and incomplete right bundle branch block (StoneCrest 66-68).

Dr. Clark Archer, an ER physician, first saw the patient in the ER at approximately 1220 (Deposition of Dr. Archer, at 31:20-32:10). Before Dr. Archer first saw the patient at approximately 1220, Nurse Bromley never saw Mr. Ruffino demonstrate a facial droop of any kind, any limited motor function or one-sided movement, or abnormal or slurred speech, and Nurse Bromley would have documented any such thing had he seen it (Deposition of Nurse Bromley, at 40:25-41:22).

Dr. Archer's Physical Exam revealed that the patient was oriented x 3, with slow, slurred speech (StoneCrest 5). His right hand was weaker than his left hand (StoneCrest 13). He had dysphasia and right arm weakness (StoneCrest 13). He as alert and his pupils were ERL (StoneCrest 14). His Glascow Coma Scale Score was 15 (StoneCrest 15). A Neurology consult was requested (StoneCrest 8). The Primary Impression by 1411 this day documented by Dr. Clark Archer, the ER physician, was TIA / CVA Syndrome, Acute (StoneCrest 9).

At 1252, a CT angiogram of the head and neck were ordered, with the reason for the ordering of this imaging being documented as "Neurological Deficit" (StoneCrest 40-41). The CTA of the head demonstrated a complete occlusion of the proximal Left MCA M1 segment. The CTA of the neck was interpreted as demonstrating no occlusion of hemodynamic stenosis (StoneCrest 61-62). This CTA was performed less than one hour after Mr. Ruffino developed a new neurological problem after the neuro checks demonstrated completely normal neurological findings at 1000, 1015, 1030, 1045, 1100, and 1200.

At 1253, a Code Stroke was called, Mr. Ruffino had some slurred speech, and another CTA was ordered (StoneCrest 22). This Code Stroke was called less than one hour after Mr. Ruffino developed a new neurological problem after the neuro checks demonstrated completely normal neurological findings at 1000, 1015, 1030, 1045, 1100, and 1200.

From 1000-1200, the patient was neurologically normal – both per the StoneCrest records and per the deposition testimony in this case from the nurse who performed six different neurological checks on the patient during this two hour time period, Nurse Bromley. Those neurological checks and corresponding documentation provide factual information that the patient was completely neurologically normal during this two hour time period.

The first time that Nurse Bromley saw any neurological abnormality in Mr. Ruffino on February 17, 2016 from 1000 forward was at approximately 1300 when the patient had a speech abnormality (Deposition of Nurse Bromley, at 98:23-99:21, 100:8-14, and 101:15-21; StoneCrest 18). The speech abnormality present at 1300 was a change since the neuro check performed at 1200 that same day (Deposition of Nurse Bromley, at 99:7-21). The first time that Nurse Bromley "had any reason to think Mr. Ruffino had a sign or symptom of stroke [was] when there was the abnormal speech around 1:00 p.m. on February 17th" (Deposition of Nurse Bromley, at 111:24-112:3).

Nurse Bromley has no memory of Mr. Ruffino having any neurological abnormality under his care prior to 1300 (Deposition of Nurse Bromley, at 103:13-17). Nurse Bromley testified that he would have documented any such abnormality if he had noticed any such thing (Deposition of Nurse Bromley, at 103:13-20).

In February 2016, Nurse Bromley could tell an ER physician if he saw a change in a patient's condition (Deposition of Nurse Bromley, at 25:5-14). In fact, he had the ability to contact

an ER physician if he thought an ER patient was in the midst of a new stroke and if he was seeing that ER patient in the first two hours of the onset of new symptoms (Deposition of Nurse Bromley, at 34:2-8). However, he did not contact an ER physician about Mr. Ruffino because he did not think that Mr. Ruffino was having a stroke during his involvement (prior to 1300) (Deposition of Nurse Bromley, at 34:15-21). For this same reason, Nurse Bromley never asked a physician to see Mr. Ruffino in the ER (Deposition of Nurse Bromley, at 39:25-40:4).

Dr. Osman Raad mentioned something to Nurse Bromley about Mr. Ruffino having a potential speech abnormality, and Nurse Bromley has no reason to think this was mentioned prior to 1300 (Deposition of Nurse Bromley, at 107:16-20).

Nurse Bromley testified that the first time he knows of anyone noticing a neurological change or abnormal neurological issue in Mr. Ruffino was at approximately 1300 (Deposition of Nurse Bromley, at 108:23-109:9). It was around 1300 when a Code Stroke was called, which was in response to that new neurological change (Deposition of Nurse Bromley, at 108:23-109:12). When the Code Stroke was called at approximately 1300, Nurse Bromley had seen the patient in a normal neurological state consistently from 1000-1200 (Deposition of Nurse Bromley, at 109:13-19).

By approximately 1300 on February 17, 2016, Nurse Bromley told Dr. Archer that Mr. Ruffino had been neurological normal from 1000-1200 that day (Deposition of Nurse Bromley, at 122:11-123:1). Therefore, Nurse Bromley remembers that he told Dr. Archer when Dr. Archer first saw the patient and requested a neuro consult that the patient had been "neurologically normal" from 1000 to 1200" (Deposition of Nurse Bromley, at 123:2-9). Nurse Bromley told Dr. Archer that the patient had been neurologically normal from 1000-1200 because Nurse Bromley thought this information would have some relevance, and he left it up to Dr. Archer to decide what

to do with that information as the physician (Deposition of Nurse Bromley, at 128:24-129:8). Nurse Bromley does not remember what Dr. Archer said or did in response to that information (Deposition of Nurse Bromley, at 128:14-23).[2]

When Mr. Ruffino had a speech abnormality when Dr. Archer saw him, Dr. Archer considered that this could have been a neurological change due to an ischemic stroke (Deposition of Dr. Archer, at 43:6-18).

The speech abnormality that Nurse Bromley documented as existing at 1400 as "expressive aphasia" was the same speech abnormality that he documented as being present at 1300 as "slurred speech" (Deposition of Nurse Bromley, at 102:4-103:1; StoneCrest 19).

At 1411, Dr. Archer electronically signed his note regarding his initial contact with Mr. Ruffino that began around 1220, and Dr. Archer chose to select a template for this note entitled "Stroke/CVA" (Deposition of Dr. Archer, at 41:25-42:25; StoneCrest 3-9).

At 1414, Mr. Ruffino was given aspirin (StoneCrest 43, 45 and 69).

At 1414, an MRI of the brain was ordered (StoneCrest 48).

At 1521, **Dr. Suresh Chitturi** dictated his Consult Report regarding the neurology consult performed by Dr. Chitturi (StoneCrest 27-28). The documented Reason for Consultation was right facial weakness and speech difficulties (StoneCrest 27). The patient had been suffering similar episodes for approximately one month, including right-sided weakness, and the events until this day lasted only 3-5 minutes and would completely resolve (StoneCrest 27). As Nurse Bromley testified, he told Dr. Archer by approximately 1300 that day that the patient had been completely neurologically normal from 1000-1200 that day (Deposition of Nurse Bromley, at 122:11-123:1).

[2] Dr. Archer testified that he does not remember and "truly cannot state" what Nurse Bromley told him about Mr. Ruffino's history or problems other than that he presented by ambulance, that there had been some dizziness on presentation, that there was a history of seizures, and that the patient did not take his Neurontin that day (Deposition of Dr. Archer, at 68:11-69:5).

Dr. Chitturi did not document any awareness that the patient was reportedly completely normal neurologically per the neuro checks performed from 1000-1200, which may not have been known by Dr. Chitturi because those neuro checks were not documented until after 1600 that day and because Dr. Archer did not tell Dr. Chitturi what Nurse Bromley had told Dr. Archer by 1300 that day – that Mr. Ruffino was neurologically normal when every neurological check was performed from 1000-1200 that day (StoneCrest 15-17). However, as Nurse Bromley testified, he told Dr. Archer by approximately 1300 that day that the patient had been completely neurologically normal from 1000-1200 that day (Deposition of Nurse Bromley, at 122:11-123:1).

Dr. Chitturi documented that the recent workup that included an MRI of the brain and possibly an MR angiogram were reportedly normal (StoneCrest 27). The patient's treating neurologist (Dr. Efobi) was treating him with gabapentin for what she diagnosed as seizures (StoneCrest 27).

On physical examination, Dr. Chitturi found that the patient had some right facial weakness, slurred speech, and expressive aphasia (StoneCrest 28). He was A&Ox3 (StoneCrest 28).

Dr. Chitturi's Assessment included "likely stroke" based on the mild right facial weakness and dysarthric speech with some mild expressive aphasia (StoneCrest 28). Dr. Chitturi again noted that, at the time of his consult, the patient was already beyond "the window for any intervention including TPA and endovascular at this time" (StoneCrest 28), and this appears to be based on a presumption by Dr. Chitturi that the patient had continued and persistent symptoms since 0800-0830, but, as Nurse Bromley testified, the patient was neurologically normal from 1000-1200 that day and Nurse Bromley told Dr. Archer by approximately 1300 that day that the patient had been

completely neurologically normal from 1000-1200 that day (Deposition of Nurse Bromley, at 122:11-123:1).

Nurse Bromley testified that the ER nurses do not talk with the neurologists (Deposition of Nurse Bromley, at 119:19-120:14). According to Nurse Bromley, the ER physician speaks with the neurologist who performs the consult regarding what the patient's neurological status has been (Deposition of Nurse Bromley, at 119:19-120:14). It is not clear why or whether Dr. Archer was unable or unwilling to talk with Dr. Chitturi, the neurologist, regarding the fact that Nurse Bromley had told Dr. Archer by 1300 that the patient was neurologically normal that same day from 1000-1200.

The patient was to be transferred to Centennial Medical Center for a higher level of care, including to be cared for in the Neuro ICU (StoneCrest 9). At 2150, Mr. Ruffino was transferred to Centennial Medical Center (StoneCrest 10).

At Centennial Medical Center, the History & Physical dictated on the morning of February 18, 2016 documented that the patient had right-sided weakness, facial droop, and was favoring his left hand (Centennial 16-18). It was noted that the patient was admitted for conservative management because the window for thrombolytics had passed prior to the arrival at Centennial (Centennial 16-18).

On February 18, 2016, a head CT was performed at Centennial that demonstrated decreased perfusion through the left MVA distribution of the parasylvian left temporal, parietal, and frontal lobes without evidence of ischemia (Centennial 51-52). Also on February 18, 2016, an MRI of the brain was performed at Centennial that demonstrated acute left-sided infarcts, mainly involving the left basal ganglia and corona radiata (Centennial 52). The Diagnosis documented on February 18, 2106 was acute thromboembolic CVA (Centennial 52).

On February 19, 2016, it was documented that the patient had made some progress via the treatment that was provided at Centennial (Centennial 50).

The February 26, 2016 Discharge Summary documents the Primary Discharge Diagnosis as acute CVA, MCA, residual dysarthria (Centennial 14). It was noted that the patient was outside the window for thrombolytics by the time he arrived via transfer to Centennial (Centennial 14).

19. When Dr. Archer identified the new neurological deficits at or soon after 1220, and knew by 1300, per Nurse Bromley's testimony, that these neurological deficits were not present from 1000-1200 and the patient was last seen neurologically normal as recently as 1200, it was within the window of time at 1220-1300 for treatment for the stroke including IV tPA and an endovascular thrombectomy to have likely provided Mr. Ruffino with a better outcome than he received without that treatment being provided. The treatment that could have been provided by Dr. Archer and/or under his direction and/or management was to administer IV tPA and to arrange for transfer to a comprehensive stroke center. Had those things been done within at least 6 hours of Dr. Archer first seeing the patient at approximately 1220, Mr. Ruffino would have had a better outcome from his stroke. That improved blood flow via such treatment being provided within 6 hours of 1200 would have likely limited or prevented the permanent brain injury that occurred as a result of the lack of such treatment causing that decreased blood flow through that vessel of the brain – thus providing a better outcome for the patient. In addition, if there were stroke symptoms present at approximately 0800-0830 on February 17, 2016 that anyone thought were persistent and continuous through when Dr. Archer first saw the patient and recognized neurological deficits by 1220-1300, it was still within 6 hours of 0800-0830 for proper treatment, as mentioned herein, to have likely provided a better outcome for this stroke patient.

FURTHER THE AFFIANT SAYETH NOT.

TROY POPE, M.D.

SWORN TO and SUBSCRIBED before me, a Notary Public in and for the said County and State on this 22 day of December, 2017.

Richard Walter Albright
Notary Public
Buncombe County, NC

NOTARY PUBLIC
My Commission Expires: 4/10/2021
Respectfully submitted,

CERTIFICATE OF SERVICE

I certify that on December _________, 2017, a true and correct copy of this document was provided to the following via the Court's electronic filing system:

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EXHIBIT 1

Troy T. Pope, MD, FACEP
67 Lula Cove Road
Weaverville, NC 28787
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Specialty Areas of Expertise

- **Over 10 years' experience as an Emergency Medicine attending physician in active practice**
- **Boarded in Emergency Medicine and Integrative and Holistic Medicine**
- **Proficient in Epic, Cerner, Wellsoft, Meditech, Medhost, Sunrise Clinical Manager, Chartmaxx, and T-system**

Current Position

MESA OF TEAMHEALTH
Emergency Medicine Attending Physician
Haywood Regional Medical Center, North Carolina, 11/2017-present
Taylor Regional Medical Center, Campbellsville, Kentucky 12/2014-present
St. Joseph Hospital, London, Kentucky 9/2013-present
Springview Hospital, Lebanon, KY 2/2013-present

Certifications

American Board of Integrative and Holistic Medicine	2011
American Board of Emergency Medicine	2006

Licensure

North Carolina Medical Board	2012-present
Kentucky Board of Medical Licensure	2012-present
Oregon Medical Board	2011-present
California Medical Board	2005-present

Education

UNIVERSITY OF KENTUCKY *Lexington, Kentucky* — 2005

- **Emergency Medicine Residency**

GEORGIA HEALTH SCIENCES UNIVERSITY:
Medical College of Georgia *Augusta, Georgia* — 2002

- **Doctor of Medicine**
  - ***cum laude***

UNIVERSITY OF VIRGINIA *Charlottesville, Virginia* — 1998

- **Bachelor of Science in Chemistry**
  - ***cum laude***

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Experience as an Emergency Medicine Physician

TEAMHEALTH
*Serve as a **Traveling Attending Emergency Physician**,*
traveling/assigned to various healthcare facilities as the staffing needs arise
Kentucky, 2012-present

Haywood Regional Medical Center November 2017-present
Somerset, Kentucky
A regional community hospital and Duke LifePoint quality affiliate. The 18-bed ED is an American College of Cardiology chest pain referring center with a psychiatric ED unit and an inpatient psychiatric floor.
•40,000 patient visits per year – 33 hours of physician and 12 hours of midlevel coverage daily

Lake Cumberland Regional Hospital April 2017-present
Somerset, Kentucky
A 295-bed community hospital and Duke LifePoint quality affiliate. The 24-bed ED with an 8 bed fast-track is an American College of Cardiology chest pain center with primary PCI for STEMI intervention as well as an advanced primary stroke center with neurosurgical services. The ED hosts residents from its two primary care residencies.
•35,000 patient visits per year – 24 hours of physician and 22 hours of midlevel coverage daily

Georgetown Community Hospital November 2016-present
Georgetown, Kentucky
A 75-bed community hospital and Duke LifePoint quality affiliate. The 18-bed ED is an American College of Cardiology chest pain referring center.
•30,000 patient visits per year – 24 hours of physician and 22 hours of midlevel coverage daily

Taylor Regional Medical Center December 2014-present
Campbellsville, Kentucky
One of two verified Level III trauma centers in Kentucky, and the longest consistently verified Level III trauma center in Kentucky with a 15 bed ED.
•30,000 patient visits per year – 24 hours of physician and 12 hours of midlevel coverage daily

Ephraim McDowell Regional Medical Center January 2014-present
Danville, Kentucky
A non-profit, 222-bed licensed hospital providing a full continuum of care to six counties throughout central Kentucky with a TJC gold star for hip & knee replacement and spine surgery, and an inpatient psychiatry unit. The 20 bed ED is a level III trauma center and boasts an American College of Cardiology chest pain center certification with primary PCI for STEMI intervention.
•45,000 patient visits per year – 36 hours of physician and 24 hours of midlevel coverage daily

St. Joseph Hospital September 2013-present
London, Kentucky
A 120-bed, nationally-ranked, award-winning general medical and surgical hospital founded in 1926 with a 24 bed ED, an 8 bed Fast-Track ED, and 24 hour Primary PCI for STEMI intervention.
•45,000 patient visits per year – 36 hours of physician and 36 hours of midlevel coverage daily

Pikeville Medical Center May 2013-present
Pikeville, Kentucky
A 300-bed regional referral center; A member of the Mayo Clinic Care Network providing 400+ specialty and subspecialty services with American College of Cardiology Atrial Fibrillation care certification. The 28 bed ED with an 8 bed fast-track ED is a Level II trauma center, American College of Cardiology chest pain receiving center with primary PCI for STEMI intervention, and an American Heart Association primary stroke center for CVA intervention.
•50,000 patient visits per year – 36 hours of physician and 36 hours of midlevel coverage daily with scribes

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Experience as an Emergency Medicine Physician *continued*

Baptist Health Richmond March 2013-present
Richmond, Kentucky
A 105-bed acute care hospital with a 20-bed fast-track ED and a cardiac cath lab with STEMI intervention.
•32,000 patient visits per year – 30 hours of physician and 30 hours of midlevel coverage daily

Clark Regional Medical Center February 2013-present
Winchester, Kentucky
A 79-bed acute care hospital and Duke LifePoint quality affiliate. The 18-bed ED is an American College of Cardiology chest pain referring center.
•35,000 patient visits per year – 24 hours of physician and 36 hours of midlevel coverage daily

Springview Medical Center February 2013-present
Lebanon, Kentucky
A 75-bed community hospital and Duke LifePoint quality affiliate. The 12-bed ED is an American College of Cardiology chest pain referring center.
•20,000 patient visits per year – 24 hours of physician coverage daily

University of Kentucky Good Samaritan Hospital February 2013-March 2016
Lexington, Kentucky
An inner-city ED with 302 licensed beds in single-occupancy rooms, and home to Kentucky's second-largest orthopedic and joint replacement program as well as UK's psychiatric hospital. The 15-bed ED had 24 hour STEMI intervention, and Advanced Comprehensive Stroke care at the nearby UK Chandler Medical Center campus.
•30,000 patient visits per year – 24 hours of physician and 24 hours of midlevel coverage daily

Bourbon Community Hospital February 2013-May 2015
Paris, Kentucky
Serving the counties of Bourbon and Nicholas, the 9 bed ED was an American College of Cardiology chest pain referring center.
•15,000 patient visits per year – 24 hours of physician coverage daily

WEATHERBY HEALTHCARE
Served as a Locum Tenens Attending Emergency Physician
Oregon, California, 2012-2013

Asante Three Rivers Medical Center July 2012-September 2012
Grants Pass, Oregon
The largest healthcare provider in the area's nine counties, providing medical care to more than 580,000 people throughout southern Oregon and northern California. The 24 bed ED was an American College of Cardiology chest pain referring center.
•35,000 patient visits per year – 44 hours of physician coverage daily

Mercy General Hospital January 2013-February 2013
Sacramento, California
A 342-bed inner-city hospital with special advocacy for the poor and underserved, and includes the nationally-recognized Dignity Health Heart & Vascular Institute with ACC atrial fibrillation care certification plus TJC heart failure and VAD accreditation. The 30 bed ED was an American Heart Association primary stroke center an American College of Cardiology chest pain center with primary PCI for STEMI intervention.
•50,000 patient visits per year – 36 hours of physician and 36 hours of midlevel coverage daily with scribes

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Experience as an Emergency Medicine Physician *continued*

SAMARITAN HEALTH SERVICES:
Good Samaritan Regional Medical Center *and* Samaritan Albany General Hospital
Served as a Staff Attending Emergency Medicine Physician
at Samaritan's two facilities in the region
Oregon, November 2011-December 2012

Samaritan Albany General Hospital November 2011-December 2012
Albany, Oregon
A 79-bed acute care facility and health center providing medical services to the greater Albany, Oregon, area since 1924. The 14-bed ED averaged 3.1 patients per hour.
•27,000 patient visits per year – 24 hours of physician coverage daily

Good Samaritan Regional Medical Center November 2011-December 2012
Corvallis, Oregon
A regional referral center and the largest hospital across three counties. The 24 bed ED was a Level II trauma center.
•35,000 patient visits per year – 36 hours of physician and 24 hours of midlevel coverage daily

THE NORTHBAY HEALTHCARE SYSTEM:
NorthBay Medical Center *and* NorthBay VacaValley Hospital
Served as a Staff Attending Emergency Medicine Physician
at NorthBay Healthcare System's two facilities
Fairfield & VacaValley, California, July 2005-October 2011

NorthBay Medical Center July 2005-October 2011
Fairfield, California
A 132-bed top-tier urban facility. The 30 bed ED was a Level III trauma center, an American College of Cardiology chest pain center with primary PCI for STEMI intervention and an American Heart Association certified primary stroke center.
●45,000 visits per year – 40 hours of physician and 24 hours of midlevel coverage, with residents

NorthBay VacaValley Hospital July 2005-October 2011
VacaValley, California
A 50-bed community hospital and sister facility to NorthBay Medical Center. The 16 bed ED transferred to the Fairfield campus for its acute trauma, STEMI, and stroke needs.
●25,000 visits per year – 24 hours of physician and 12 hours of midlevel coverage daily

Publications

1. Pope, T.T., *Maxillofacial and Neck Trauma.* In Stone CK, Humphries RL (eds). Current Emergency Diagnosis and Treatment 6th Edition, McGraw Hill Book Company, New York, 2008.
2. Pope T.T.,& Rock, T.C., *Maxillofacial and Neck Trauma.* In Stone CK, Humphries RL (eds). Essentials of Emergency Medicine Diagnosis and Treatment 1st Edition, McGraw Hill Book Company, New York, 2005.
3. Pope T.T., & Rock, T.C., *Vertebral Column and Spinal Cord Trauma.* In Stone CK, Humphries RL (eds). Essentials of Emergency Medicine Diagnosis and Treatment 1st Edition, McGraw Hill Book Company, New York, 2005.

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Professional Memberships & Associations

American Board of Emergency Medicine (ABEM)	**2006-present**
Academy of Integrative Health & Medicine (AIHM)	**2012-present**
American College of Emergency Physicians (ACEP)	**2013-present**
Fellow of the American College of Emergency Physicians (FACEP)	**2017-present**

Committee Appointments

***Sepsis Committee** – NorthBay Healthcare, Fairfield, CA* **2008-2011**

Appointed to the NorthBay HealthCare's Sepsis Committee to serve as the Sepsis ED Physician Director. Designed sepsis protocol and algorithms for the ED. Worked with other committee members to identify ways to improve the provision of timely care to this large segment of the patient population and to discuss the upgrading of sepsis and insulin management, and sedation and pain policies.

***Critical Care Committee** – NorthBay Healthcare, Fairfield, CA* **2007-2011**

Served as the representative Emergency Department Physician member on this committee that was created to review and make suggestions or revisions regarding all policies and procedures that affect patient care in the critical care units at NorthBay Healthcare, including the Emergency Department. Collaborated with intensivists, pulmonologists, cardiologists, neurologists, hospitalists, nephrologists, and other committee members to discuss, identify, and actively pursue quality goals, including improvement of mortality outcomes, length of stay and improved functionality of patients leaving the ICU.

***Code Blue Committee** – NorthBay Healthcare, Fairfield, CA* **2007-2011**

Worked with committee to review code paperwork and current processes, and initiate improvement regarding protocols to follow and training to implement. Helped create and implement the Rapid Response Team.

***Emergency Department Throughput Committee** – NorthBay Healthcare, Fairfield, CA* **2007-2011**

Collaborated with clinical staff, house staff, and nursing staff regarding the ED's ability to increase patient satisfaction by improving front-end throughput from the ED to disposition.

REVISED: 12/21/2017

COLLECTIVE EXHIBIT 2

ORIGINAL ARTICLE

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke

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ABSTRACT

BACKGROUND

Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment. We evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation.

METHODS

We randomly assigned participants to receive standard care (control group) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group). Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on computed tomography (CT) and CT angiography were excluded. Workflow times were measured against predetermined targets. The primary outcome was the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention would lead to lower scores on the modified Rankin scale than would control care (shift analysis).

RESULTS

The trial was stopped early because of efficacy. At 22 centers worldwide, 316 participants were enrolled, of whom 238 received intravenous alteplase (120 in the intervention group and 118 in the control group). In the intervention group, the median time from study CT of the head to first reperfusion was 84 minutes. The rate of functional independence (90-day modified Rankin score of 0 to 2) was increased with the intervention (53.0%, vs. 29.3% in the control group; P<0.001). The primary outcome favored the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; P=0.04). Symptomatic intracerebral hemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (P=0.75).

CONCLUSIONS

Among patients with acute ischemic stroke with a proximal vessel occlusion, a small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment improved functional outcomes and reduced mortality. (Funded by Covidien and others; ESCAPE ClinicalTrials.gov number, NCT01778335.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hill at the Calgary Stroke Program, Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Foothills Hospital, Rm. 1242A, 1403 29th Street NW, Calgary, AB T2N 2T9, Canada, or at michael.hill@ucalgary.ca.

Drs. Goyal and Hill contributed equally to this article.

*A complete list of sites and investigators in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 11, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1414905

Ischemic stroke is a devastating condition with a high burden of neurologic disability and death. As a systemic treatment, intravenous alteplase has been shown to be better than conservative care.[1,2] Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment.[3,4] The major reason for the limited efficacy of alteplase is the modest rate of early reperfusion among patients with a large-vessel occlusion.[5,6]

Local treatment of large-vessel occlusion began with intraarterial delivery of thrombolytic drugs.[7] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study was the first positive trial of endovascular treatment involving patients with angiographically visualized occlusion of the middle cerebral artery.[8] Unfortunately, subsequent trials did not confirm the clinical benefit even with the addition of first-generation thrombectomy devices.[3,9,10] Key lessons learned from these previous trials are the need for proof of proximal vessel occlusion,[11] rapid and effective imaging methods to exclude patients with a large infarct core,[12-14] an efficient workflow to achieve fast recanalization,[15,16] and high reperfusion rates.[17-19]

Recent studies have shown the superiority of retrievable stents over the previous generation of thrombectomy devices.[17,18] The recently reported Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) used this technology, and the results of that trial showed clinical benefit with endovascular treatment.[4] The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was designed to test whether patients with acute ischemic stroke, who were selected on the basis of results of computed tomography (CT) and CT angiography (CTA), would benefit from rapid endovascular treatment involving contemporary endovascular techniques.[20]

METHODS

TRIAL DESIGN

The ESCAPE trial was a multicenter, prospective, randomized, open-label, controlled trial with blinded outcome evaluation (PROBE design).[20] Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group) (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). This academic-investigator–initiated trial was designed to answer a practical question regarding a patient with acute ischemic stroke who has just undergone neurovascular imaging with noncontrast CT and CTA: "Should this patient undergo endovascular thrombectomy?" (Fig. S3 in the Supplementary Appendix).

The trial was monitored by an independent data and safety monitoring board. The study funders, including Covidien, were not involved in the design or conduct of the study, the preparation or review of the protocol, the collection or analysis of the data, or the preparation or review of the manuscript. All the authors collected data, provided comments on the analysis, contributed to the writing of the manuscript, and were independent of the sponsors. All the authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol, available at NEJM.org.

Sites were selected for participation after visits by the principal investigators and documentation of fast treatment times and efficient workflow. The principal investigator at each site signed a formal letter stating a commitment to attempt to enroll consecutive patients who were eligible for the ESCAPE trial.[21] The ethics board at each site approved the trial. In jurisdictions where it was permitted, the consent process was deferred when the participant lacked the capacity to provide consent and a legally authorized representative was unavailable.

Randomization was performed with the use of a real-time, dynamic, Internet-based, randomized minimization procedure (minimal sufficient balance method)[22] to achieve distribution balance with regard to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater stroke severity), site of arterial occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with respect to intravenous alteplase treatment. The ASPECTS scale is a 10-point scoring system to quantify early ischemic changes in the middle-cerebral-artery territory, with a score of 10 indicating normal and 1 point subtracted for each abnormal region (details are available at www.aspectsinstroke.com).[23,24]

PARTICIPANTS

Eligible participants were adults (no upper-age limit) with a disabling ischemic stroke who had been functioning independently in the community (score on the Barthel Index [range, 0 to 100, with higher scores indicating a greater ability to complete activities of daily living] ≥90) before the stroke. Enrollment could occur up to 12 hours after the onset of stroke symptoms. Noncontrast CT and CTA (preferably multiphase) were performed to identify participants with a small infarct core, an occluded proximal artery in the anterior circulation, and moderate-to-good collateral circulation.[14,25-28] Multiphase CTA is less vulnerable to patient motion than CT perfusion, requires no additional contrast, and allows for quick determination of collateral status[12] (Fig. S2 in the Supplementary Appendix). The use of magnetic resonance imaging for patient selection was discouraged. A small infarct core was defined as an ASPECTS of 6 to 10. Proximal artery occlusion in the anterior circulation was defined as occlusion of the middle-cerebral-artery trunk and its immediate branches, with or without intracranial occlusion of the internal carotid artery (Fig. S4 in the Supplementary Appendix). Moderate-to-good collateral circulation was defined as the filling of 50% or more of the middle-cerebral-artery pial arterial circulation on CTA (preferably on multiphase CTA).

Imaging was performed at the endovascular center; for patients transferred from other hospitals, imaging was repeated. Before and during screening, participants were treated with intravenous alteplase when clinically appropriate as part of standard care (Fig. S3 in the Supplementary Appendix). We did not keep a log of patients who were screened for the trial.[29]

TREATMENTS

Participants in the intervention group underwent rapid endovascular treatment. A cerebral angiogram was obtained. The neurointerventionist used available thrombectomy devices to achieve reperfusion. The use of retrievable stents was recommended. During thrombus retrieval, suction through a balloon guide catheter in the relevant internal carotid artery was also recommended. The control group received the current standard of care as described in the Canadian or local guidelines for the management of acute stroke[30,31] (see the Methods section in the Supplementary Appendix). Participants in both groups received intravenous alteplase within 4.5 hours after the onset of stroke symptoms if they met accepted local guidelines for intravenous alteplase treatment.

Weekly monitoring of imaging and treatment speed, with regular feedback to sites by teleconference, ensured adherence to participant eligibility criteria and workflow metrics. Guidance on rapid, effective endovascular treatment and high-quality imaging methods was provided. The target time from study noncontrast CT to groin puncture was 60 minutes or less and from study noncontrast CT to first reperfusion (defined as first reflow in the middle cerebral artery) was 90 minutes or less. These aggressive targets were chosen to emphasize speed and ensure rapid imaging acquisition and interpretation, quick transfer of patients to the angiography suite, and fast reperfusion. If there were clear patient-related factors (e.g., vessel tortuosity) or workflow factors (e.g., unavailability of the intervention team) that would prevent meeting the time targets, it was recommended that patients not be enrolled.

CLINICAL ASSESSMENTS AND OUTCOMES

All participants had standard assessments of demographic characteristics, medical history, laboratory values, and stroke severity (NIHSS score). Details of the assessments have been published previously[20] and are also available in the study protocol. The primary outcome — the score on the modified Rankin scale at 90 days after randomization — was assessed by trained personnel who were unaware of the treatment-group assignments. The modified Rankin scale is a graded interval scale (range, 0 [no symptoms] to 6 [death]) for the assessment of neurologic functional disability.[32] Secondary and safety outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death. Interpretation of the imaging was performed at an external core laboratory by personnel who were unaware of the treatment-group assignments (when they interpreted the CT images), clinical data, and outcomes. External, independent clinical monitors validated the clinical data.

STATISTICAL ANALYSIS

The trial was powered to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between the intervention and control groups, with scores of 5 (bedbound with severe disability) and 6 (death) combined, with

the assumption that the differential effect would lead to a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 1.8. A total required sample of 500 participants was anticipated. One formal interim analysis after the enrollment of 300 participants was planned. The stopping rule for efficacy was defined with the use of O'Brien–Fleming boundaries on the binary outcome of a modified Rankin score at 90 days of 0 to 2 versus 3 to 6.[20] The primary analysis was unadjusted and was performed in the intention-to-treat population. P values of less than 0.05 were considered to indicate statistical significance, and all tests of hypotheses were two-sided. No adjustments were made for multiple comparisons. Adjusted estimates of effect were calculated, with adjustment for age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion (internal carotid artery plus middle cerebral artery vs. middle cerebral artery only), and status with respect to intravenous alteplase treatment (yes vs. no). The assessment of effect modification (heterogeneity of treatment effect) was performed with the inclusion of multiplicative interaction terms. All analyses were performed with the use of Stata software, version 12.1 (StataCorp). Figures were drawn with the use of both Stata software, version 12.1, and R software (R Development Core Team 2014, www.r-project.org). Further details are provided in the statistical analysis plan (available at NEJM.org).

Table 1. Baseline Characteristics and Process Measures.*

Variable	Intervention (N=165)	Control (N=150)
Demographic characteristics		
Age — yr		
Median	71	70
Interquartile range	60–81	60–81
Female sex — no. (%)	86 (52.1)	79 (52.7)
White race — no. (%)†	144 (87.3)	131 (87.3)
Medical history — no. (%)		
Hypertension	105 (63.6)	108 (72.0)
Diabetes mellitus	33 (20.0)	39 (26.0)
Atrial fibrillation	61 (37.0)	60 (40.0)
Clinical characteristics		
NIHSS score‡		
Median	16	17
Interquartile range	13–20	12–20
Systolic blood pressure at hospital arrival — mm Hg		
Median	147	146
Interquartile range	131–159	125–169
Glucose level at hospital arrival — mmol/liter§		
Median	6.6	6.7
Interquartile range	5.8–7.7	5.7–7.8
Imaging characteristics		
ASPECTS on CT — median (interquartile range)¶	9 (8–10)	9 (8–10)
Location of occlusion on CTA — no./total no. (%)‖		
ICA with involvement of the M1 middle-cerebral-artery segment	45/163 (27.6)	39/147 (26.5)
M1 or all M2 middle-cerebral-artery segments	111/163 (68.1)	105/147 (71.4)
Single M2 middle-cerebral-artery segment	6/163 (3.7)	3/147 (2.0)
Ipsilateral cervical carotid occlusion — no. (%)	21 (12.7)	19 (12.7)

Table 1. (Continued.)

Variable	Intervention (N=165)	Control (N=150)
Process times — min**		
Stroke onset to randomization		
Median	169	172
Interquartile range	117–285	119–284
Stroke onset to study CT		
Median	134	136
Interquartile range	77–247	76–238
Stroke onset to start of IV alteplase		
Median	110	125
Interquartile range	80–142	89–183
Study CT to groin puncture		
Median	51	
Interquartile range	39–68	
Study CT to first reperfusion††		
Median	84	
Interquartile range	65–115	
Stroke onset to first reperfusion††		
Median	241	
Interquartile range	176–359	
Treatment with IV alteplase — no. (%)	120 (72.7)	118 (78.7)

* The intervention group was assigned to endovascular treatment plus standard care, and the control group was assigned to standard care alone. CT denotes computed tomography, CTA CT angiography, ICA internal carotid artery, and IV intravenous.

† Race was self-reported.

‡ Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

§ To convert the values to milligrams per deciliter, divide by 0.05551.

¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores ranges from 0 to 10, with higher scores indicating a smaller infarct core (details are available at www.aspectsinstroke.com).

‖ In one participant in the intervention group, the location of the occlusion on CTA was not determined by the core laboratory. Occlusion of the ICA with involvement of the M1 middle-cerebral-artery segment could occur with or without involvement of the A1 anterior-cerebral-artery segment (see Fig. S4 in the Supplementary Appendix). The M1 middle-cerebral-artery segment extends from the origin to the site of bifurcation or trifurcation (the anterior temporal artery is considered a branch of the M1 segment). The M2 middle-cerebral-artery segments extend from the site of bifurcation or trifurcation to the origin of the cortical branches.

** For the time from stroke onset to the start of IV alteplase, data were missing for 1 patient in the intervention group. For the time from study CT to groin puncture, 161 patients were included in the analysis. For the time from study CT to first reperfusion and the time from stroke onset to first reperfusion, 145 patients were included in the analysis.

†† First reperfusion was defined as the first visualization of reflow in the middle cerebral artery, usually on deployment of a retrievable stent.

RESULTS

EARLY TERMINATION OF THE STUDY

An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy (see the Methods section in the Supplementary Appendix). The ESCAPE trial was stopped early on the advice of the data and safety monitoring board because the prespecified boundary for efficacy had been crossed.

PATIENTS

At 22 centers in Canada (11 centers), the United States (6), South Korea (3), Ireland (1), and the

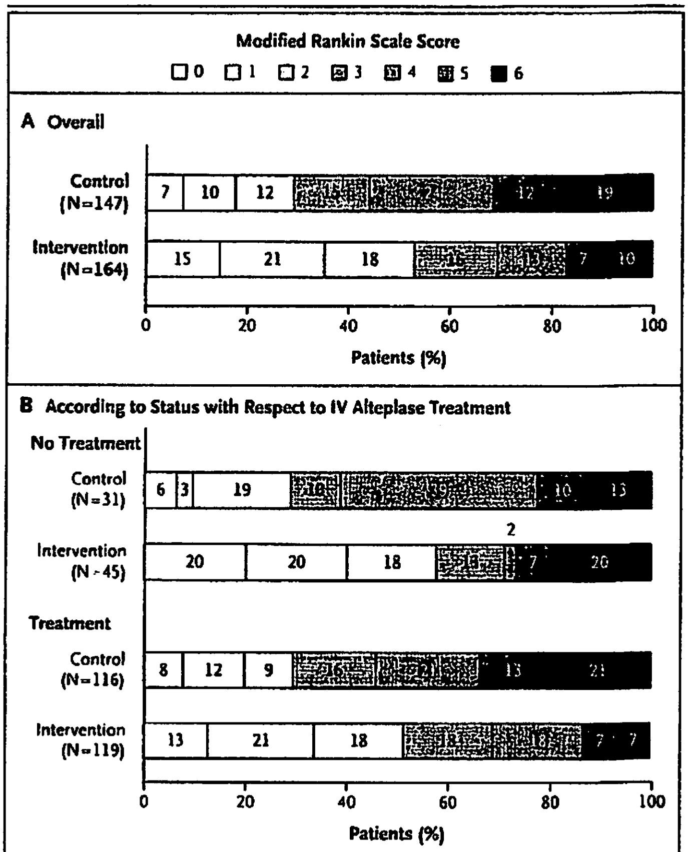

Figure 1. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect (P=0.89 for interaction by the Wald test).

United Kingdom (1), a total of 316 participants underwent randomization before the trial was stopped: 165 participants were assigned to the intervention group, 150 participants were assigned to the control group, and 1 participant was excluded owing to improper consent procedures. The trial enrolled 1.44 participants per center per month from February 2013 through October 2014. One participant in the control group crossed over to receive endovascular treatment. In the intervention group, 14 participants did not receive any interventional therapy. Four participants (1.3%) were lost to follow-up; missing data on outcomes in these participants were not imputed (Fig. S1 in the Supplementary Appendix).

Baseline characteristics were similar in the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix). Imaging protocol violations, identified by personnel who interpreted the images at the core laboratory, occurred in 26 participants (8.3%): 11 of 308 participants in whom the ASPECTS could be evaluated (3.6%) had a score of less than 6 on the ASPECTS scale, 20 of 315 participants (6.3%) had poor collateral circulation, and 14 of 315 participants (4.4%) had inappropriate target-vessel occlusion (some participants had >1 protocol violation). Collateral circulation was assessed with the use of multiphase CTA in a majority of participants. A total of 56 participants (17.8%) were enrolled with deferral of consent procedures. Monitoring of appropriate source documentation materials (with regard to informed consent, inclusion and exclusion criteria, randomization information, demographic characteristics, and assessments at baseline [NIHSS score and Barthel Index score] and at day 90 [modified Rankin score, NIHSS score, and Barthel Index score]) was completed for all randomly assigned participants.

PRIMARY OUTCOME

Analysis of the primary end point showed a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 2.6 (95% confidence interval [CI], 1.7 to 3.8) favoring the intervention (P<0.001) (Fig. 1A and Table 2). The median 90-day modified Rankin score was 2 in the intervention group and 4 in the control group (P<0.001). The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (rate ratio, 1.8; 95% CI, 1.4 to 2.4; P<0.001). Mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group (rate ratio, 0.5; 95% CI, 0.3 to 1.0; P=0.04) (Fig. S5 in the Supplementary Appendix). The rate of symptomatic intracerebral hemorrhage was 3.6% in the intervention group and 2.7% in the control group (rate ratio, 1.4; 95% CI, 0.4 to 4.7; P=0.75). Device-related or procedural complications were observed in 18 patients: 4 had a

Table 2. Primary and Secondary Efficacy Outcomes.

Outcome	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†
Primary outcome: modified Rankin score at 90 days‡				Common odds ratio	2.6 (1.7–3.8)	3.1 (2.0–4.7)
Modified Rankin score of 0–2 at 90 days — no./total no. (%)§	87/164 (53.0)	43/147 (29.3)	23.8 (13.2–34.4)	Rate ratio	1.8 (1.4–2.4)	1.7 (1.3–2.2)
NIHSS score of 0–2 at 90 days — no./total no. (%)	79/153 (51.6)	31/134 (23.1)	28.4 (17.8–39.2)	Rate ratio	2.2 (1.6–3.2)	2.1 (1.5–3.0)
Barthel Index score of 95–100 at 90 days — no./total no. (%)¶	94/163 (57.7)	49/146 (33.6)	24.1 (13.3–34.9)	Rate ratio	1.7 (1.3–2.2)	1.7 (1.3–2.2)
TICI score of 2b or 3 at final angiogram — no./total no. (%)‖	113/156 (72.4)					
Modified AOL score of 2 or 3 — no./total no. (%)**		43/138 (31.2)				
NIHSS score at 24 hours — median (interquartile range)††	6 (3–14)	13 (6–18)		Beta coefficient	4.0 (2.2–5.8)	4.1 (2.6–5.6)
NIHSS score at 90 days — median (interquartile range)††	2 (1–8)	8 (3–19)		Beta coefficient	6.5 (3.2–9.8)	6.5 (3.5–9.6)
EQ-5D visual-analogue scale score at 90 days — median (interquartile range)††‡‡	80 (60–90)	65 (50–80)		Beta coefficient	9.4 (3.5–15.2)	9.9 (3.8–16.0)

* Differences (intervention group − control group) are shown as percentage points.

† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.

‡ The primary analysis involved 164 participants in the intervention group and 147 participants in the control group. Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of improvement of 1 point on the modified Rankin scale, with a common odds ratio greater than 1 favoring the intervention. The proportional odds assumption was tested and found to be valid.

§ A modified Rankin score of 0 to 2 indicates functional independence.

¶ The Barthel Index is an ordinal scale for measuring performance of activities of daily living. Scores range from 0 to 100, with 0 indicating severe disability and 95 or 100 no disability that interferes with daily activities.

‖ A Thrombolysis in Cerebral Infarction (TICI) score of 2b or 3 indicates successful reperfusion (see Table S3 in the Supplementary Appendix).

** A modified Arterial Occlusive Lesion (AOL) score of 2 or 3 indicates partial or complete recanalization (see Table S3 in the Supplementary Appendix).

†† Treatment effect was estimated with the use of simple linear regression.

‡‡ The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale is a continuous scale measure of self-reported quality of life. Scores range from 0 to 100, with 0 indicating the worst possible quality of life and 100 the best possible quality of life.

serious adverse event and 14 had a nonserious adverse event (Table 3, and Table S2 in the Supplementary Appendix).

SECONDARY OUTCOMES AND SUBGROUP ANALYSES

Secondary clinical and imaging end points favored the intervention group. The rate of patients with a score on the Barthel Index of 95 to 100 at 90 days was 57.7% in the intervention group versus 33.6% in the control group, the rate of patients with a 90-day NIHSS score of 0 to 2 was 51.6% versus 23.1%, and the median 90-day score on the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale (range, 0 to 100, with higher scores indicating better quality of life) was 80 versus 65 (Table 2).

There was no evidence of heterogeneity of effect across any of the prespecified subgroups (defined according to age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to alteplase treatment) or according to the presence or absence of cervical carotid occlusion. All variables showed a direction of effect in favor of the intervention (Fig. 2, and Fig. S6 in the Supplementary Appendix). However, the absolute proportion of good outcomes varied substantially according to subgroup (Fig. 1B, and Fig. S7 in the Supplementary Appendix).

Table 3. Reported Serious Adverse Events.

Event	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (−2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group − control group) are shown as percentage points.

† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.

‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).

§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.

¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

A total of 49 patients underwent randomization 6 or more hours after stroke onset; in the analysis of a modified Rankin score of 0 to 2 at 90 days, the direction of effect favored the intervention in these patients (rate ratio, 1.7; 95% CI, 0.7 to 4.0), but the between-group difference was not significant.

Of 165 participants assigned to the intervention group, 151 (91.5%) underwent endovascular treatment, and 120 (72.7%) received intravenous alteplase. General anesthesia was used in 15 participants (9.1%). Retrievable stents were used in 130 of the 151 participants (86.1%) who underwent an endovascular procedure; 100 of these 130 participants (77.0%) received a Solitaire stent (Covidien). In the intervention group, the median time from symptom onset to first reperfusion was 241 minutes (interquartile range, 176 to 359), the median time from study CT to first reperfusion was 84 minutes (interquartile range, 65 to 115), and the median time from groin puncture to first reperfusion was 30 minutes (interquartile range, 18 to 46). Successful reperfusion (as defined by a core-laboratory–adjudicated Thrombolysis in Cerebral Infarction [TICI] score of 2b or 3, indicating complete filling of the expected vascular territory) was observed in 113 of 156 participants (72.4%) in the intervention group: 79 of 112 participants (70.5%) who received intravenous alteplase and 34 of 44 participants (77%) who did not. (For details on the TICI scale, see Table 3 in the Supplementary Appendix.)

In the control group, follow-up CTA was performed in 138 participants (median time from symptom onset to follow-up CTA, 425 minutes [interquartile range, 355 to 564]). Successful recanalization (as defined by a core-laboratory–adjudicated modified Arterial Occlusive Lesion score of 2 or 3 on CTA, indicating partial or complete recanalization of the occluded artery) was observed in 43 of 138 participants (31.2%): 41 of 110 (37.3%) who received intravenous alteplase and 2 of 28 (7%) who did not. (For details on the modified Arterial Occlusive Lesion scale, see Table S3 in the Supplementary Appendix.)

DISCUSSION

We found that among participants with acute ischemic stroke with a small infarct core, a proximal intracranial occlusion in the anterior circulation, and moderate-to-good intracranial collateral circulation, rapid endovascular treatment improved the clinical outcome and reduced mortality. The trial confirms the benefit of endovascular treatment reported recently in the MR CLEAN trial.[4]

The ESCAPE trial attempted to deliver rapid endovascular therapy to patients who were selected for inclusion on the basis of imaging. Post hoc analysis of the Interventional Management of Stroke (IMS) III trial and the Solitaire FR Thrombectomy for Acute Revascularization (STAR) trial showed that achieving faster reperfusion, as

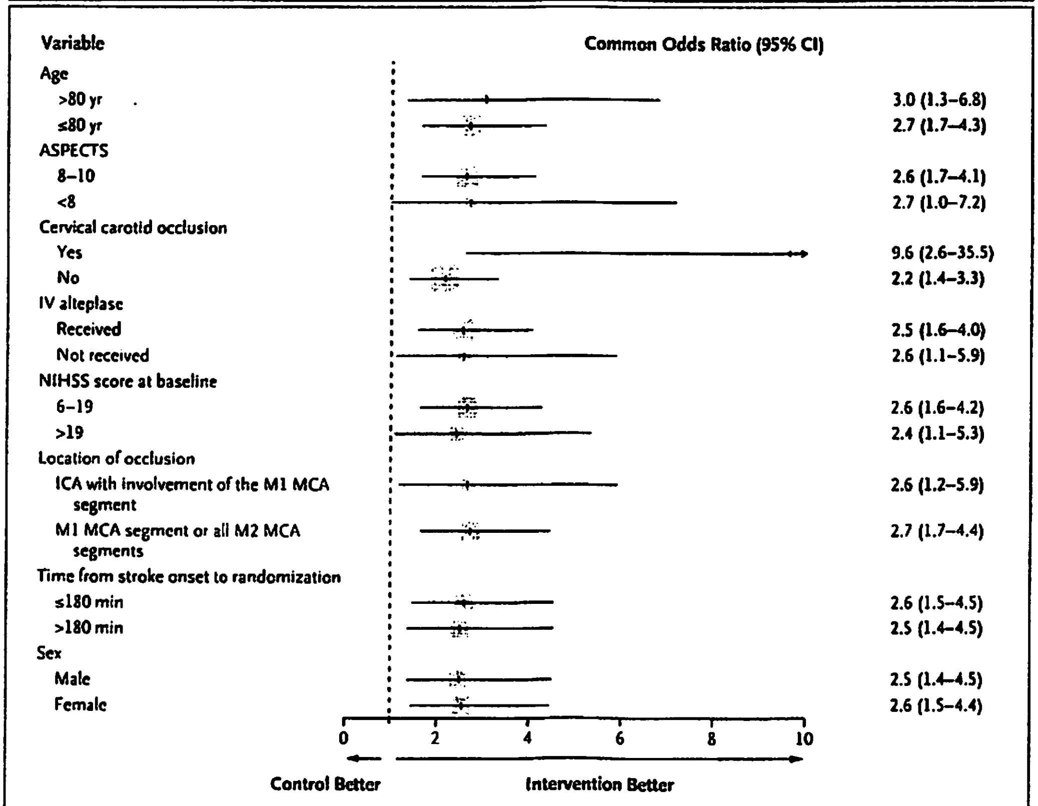

Figure 2. Subgroup Analyses.

A forest plot shows that the difference in the primary clinical outcome (common odds ratio indicating the odds of improvement of one point on the modified Rankin scale at 90 days, analyzed with the use of ordinal logistic regression) favored the intervention group across all prespecified subgroups. The thresholds for age and National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe neurologic deficits) were chosen at the 75th percentile, and the threshold for time from stroke onset to randomization was chosen just above the median. The threshold for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating a smaller infarct core) was prespecified. For cervical carotid occlusion, P=0.049 for interaction by the Wald test. Other P values were greater than 0.10 for interaction. ICA denotes internal carotid artery, and MCA middle cerebral artery.

compared with slower reperfusion, was associated with a better clinical outcome.[16,33] The ESCAPE trial achieved shorter interval times than those seen in past trials, with a median time from study noncontrast CT to first reperfusion of 84 minutes. A prespecified efficiency target for the time from noncontrast CT to reperfusion encouraged fast image acquisition and interpretation and fast decision making.[16,34-37] Critical to the achievement of rapid treatment was parallel decision making and action. For example, participants in the intervention group underwent groin puncture while alteplase was being infused, and complete reperfusion was achieved in some participants before the alteplase infusion was finished. The primary emphasis was on achieving early reperfusion.[15,16,34,35]

Imaging-related selection criteria focused on the population with a small infarct core at baseline, which was defined by both modest early ischemic change on noncontrast CT and moderate-to-good collateral circulation distal to the occlusion.[26] A new technique of collateral assessment, multiphase CTA, was used in a majority of patients (Fig. S2 in the Supplementary Appendix).[12] This imaging approach resulted in a low number of imaging protocol violations and enabled the meeting of workflow time targets.

There was no evidence of heterogeneity of treatment effect across prespecified subgroups.

Endovascular treatment appeared to benefit all ages (the oldest person enrolled in the trial was 93 years of age), both sexes, patients with moderate strokes and those with severe strokes, patients who received intravenous alteplase and those who did not, and patients with and those without occlusion in the internal carotid artery (Fig. 2, and Fig. S6 in the Supplementary Appendix). Although eligibility criteria allowed enrollment up to 12 hours after symptom onset, the median time from symptom onset to first reperfusion was 241 minutes. A total of 49 participants (15.5%) underwent randomization 6 or more hours after symptom onset, and the study was not powered to assess endovascular therapy among patients presenting 6 to 12 hours after symptom onset.

The incidence of asymptomatic hemorrhagic infarction was greater in the intervention group than in the control group (Table S2 in the Supplementary Appendix), possibly owing to early reperfusion.[38] The rate of more serious parenchymal hematomas or symptomatic hemorrhage was not higher in the intervention group than in the control group. Device-related or procedural complications were uncommon.

MR CLEAN and the ESCAPE trial showed benefit and low complication rates with endovascular treatment that was performed predominantly with retrievable stents. Factors that distinguish the ESCAPE trial from MR CLEAN and prior trials of endovascular treatment for stroke include the use of imaging to exclude participants with a large infarct core and poor collateral circulation, a shorter interval from symptom onset to treatment initiation, a low rate of general anesthesia (9% in the ESCAPE trial vs. 38% in MR CLEAN), and a higher rate of successful reperfusion (TICI score of 2b or 3). The longer time from alteplase administration to randomization (approximately 114 minutes) in MR CLEAN indicated that most patients underwent randomization after the alteplase infusion was completed.[4] These differences may account for the higher proportions of good outcomes and the larger effect size observed in the ESCAPE trial.

There are limitations of our study. First, we purposefully did not require screening logs (which tend to yield poor-quality data) and cannot provide an estimate of how many patients were ineligible on the basis of imaging criteria. Second, a majority of participants were enrolled at selected endovascular centers that are capable of implementing efficient workflow and imaging processes. This level of efficiency and expertise is not currently widespread, which limits the immediate generalizability of our results. Although the time targets used in our trial may appear daunting, the history of intervention for acute coronary syndromes suggests that such efficiency in workflow is widely attainable.[35,39,40]

In conclusion, the ESCAPE trial, in which fast and efficient workflow, innovative imaging, and effective thrombectomy devices were used, provides evidence of the benefit of endovascular treatment in patients with moderate-to-severe ischemic stroke.

Supported by Covidien through an unrestricted grant to the University of Calgary. Also supported by the University of Calgary (Hotchkiss Brain Institute, the Department of Clinical Neurosciences and Calgary Stroke Program, and the Department of Radiology), Alberta Innovates–Health Solutions, the Heart and Stroke Foundation of Canada, and Alberta Health Services.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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ORIGINAL ARTICLE

Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection

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ABSTRACT

BACKGROUND

Trials of endovascular therapy for ischemic stroke have produced variable results. We conducted this study to test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes.

METHODS

We randomly assigned patients with ischemic stroke who were receiving 0.9 mg of alteplase per kilogram of body weight less than 4.5 hours after the onset of ischemic stroke either to undergo endovascular thrombectomy with the Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All the patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. The coprimary outcomes were reperfusion at 24 hours and early neurologic improvement (≥8-point reduction on the National Institutes of Health Stroke Scale or a score of 0 or 1 at day 3). Secondary outcomes included the functional score on the modified Rankin scale at 90 days.

RESULTS

The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that had undergone reperfusion at 24 hours was greater in the endovascular-therapy group than in the alteplase-only group (median, 100% vs. 37%; P<0.001). Endovascular therapy, initiated at a median of 210 minutes after the onset of stroke, increased early neurologic improvement at 3 days (80% vs. 37%, P=0.002) and improved the functional outcome at 90 days, with more patients achieving functional independence (score of 0 to 2 on the modified Rankin scale, 71% vs. 40%; P=0.01). There were no significant differences in rates of death or symptomatic intracerebral hemorrhage.

CONCLUSIONS

In patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the Solitaire FR stent retriever, as compared with alteplase alone, improved reperfusion, early neurologic recovery, and functional outcome. (Funded by the Australian National Health and Medical Research Council and others; EXTEND-IA ClinicalTrials.gov number, NCT01492725, and Australian New Zealand Clinical Trials Registry number, ACTRN12611000969965.)

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*A complete list of investigators in the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 11, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1414792

THE RESULTS OF THE MULTICENTER RANdomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial,[1] which showed reduced disability among patients with ischemic stroke who were treated with endovascular thrombectomy in addition to standard care, represent an advance in stroke care. The MR CLEAN study followed several trials that had neutral findings with respect to the use of endovascular thrombectomy.[2-4] In the largest of these trials, the Interventional Management of Stroke 3 (IMS-3) study, investigators compared the administration of 0.9 mg of alteplase per kilogram of body weight to a bridging strategy of the use of alteplase (at a dose of 0.6 mg per kilogram for most of the trial) followed by endovascular therapy. The IMS-3 trial was halted for futility after 656 patients had been enrolled.[2]

Potential contributors to the neutral results of previous studies include relatively low rates of angiographic reperfusion, delays in achieving reperfusion, and the lack of patient selection with the use of advanced imaging to ensure the presence of vessel occlusion and salvageable brain tissue. None of the previous studies raised any safety concerns, with rates of symptomatic hemorrhage of approximately 6% in both the alteplase group and the endovascular-therapy group. More recent advances in device technology have significantly improved the speed and efficacy of recanalization.[5-7]

Computed tomographic (CT) perfusion imaging can indicate the extent of irreversibly injured brain in the ischemic core and potentially salvageable but hypoperfused ischemic penumbra.[8-11] Furthermore, CT perfusion imaging has evolved, and fully automated, standardized volumetric processing can now be rapidly performed in the context of a multicenter clinical trial.[12,13]

In the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) trial, we sought to test the hypothesis that patients with anterior circulation ischemic stroke who are selected with a dual target of vessel occlusion and evidence of salvageable tissue on perfusion imaging within 4.5 hours after the onset of stroke will have improved reperfusion and early neurologic improvement when treated with early endovascular thrombectomy with the use of the Solitaire FR (Flow Restoration) stent retriever after intravenous administration of alteplase, as compared with the use of alteplase alone. The release of the MR CLEAN trial results prompted the data and safety monitoring board for our study to review the data, and the trial was stopped early because efficacy was clearly shown.

METHODS

TRIAL DESIGN AND OVERSIGHT

The EXTEND-IA trial was an investigator-initiated, multicenter, prospective, randomized, open-label, blinded-end-point study involving patients with ischemic stroke who were receiving intravenous alteplase within 4.5 hours after stroke onset. Details of the methods used in the trial have been published previously.[14] The study protocol is available with the full text of this article at NEJM.org.

The design, analysis, and data collection for the trial were performed by members of the executive committee and investigators at the study sites (see the Supplementary Appendix, available at NEJM.org). The first author wrote the first draft of the manuscript. All the investigators vouch for the accuracy and completeness of the presented data and fidelity of the report to the study protocol. Covidien supplied the Solitaire FR device and an unrestricted grant to support trial infrastructure, but the company was not involved in the study design or conduct or in the preparation of the manuscript, except to review the protocol to ensure that the specified use of devices in the study followed the approved instructions for use.

STUDY PATIENTS

We planned to enroll 100 patients at 14 centers in Australia and New Zealand. Patients were eligible if they could receive intravenous alteplase within 4.5 hours after the onset of anterior circulation ischemic stroke and had occlusion of the internal carotid artery or of the first or second segment of the middle cerebral artery, as seen on CT angiography. In addition, CT perfusion imaging, which was processed with the use of fully automated software (RAPID, noncommercial research version, Stanford University),[12,13] was used to identify potentially salvageable brain tissue. Brain tissue at risk for infarction ("ischemic penumbra") was distinguished from minimally hypoperfused tissue if the time to maximum (Tmax) delay was more than 6 seconds.[15] Irreversibly injured brain ("ischemic core") was diagnosed if the relative

cerebral blood flow was less than 30% of that in normal tissue.[10]

Endovascular therapy had to be initiated (groin puncture) within 6 hours after stroke onset and completed within 8 hours after onset. There were no restrictions on age or clinical severity, as assessed according to the score on the National Institutes of Health Stroke Scale (NIHSS), which ranges from 0 (normal) to 42 (death). However, patients were required to have functional independence before the stroke episode, which was defined as a score of less than 2 on the modified Rankin Scale, which ranges from 0 (normal) to 6 (death).

The study was approved by the institutional ethics committee at each study site. Written informed consent was obtained from patients or a legal representative before enrollment. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY TREATMENTS

All patients received alteplase at a dose of 0.9 mg per kilogram as standard care. Patients were randomly assigned in a 1:1 ratio to receive either alteplase plus endovascular therapy (endovascular-therapy group) or no further therapy (alteplase-only group) by means of a centralized website and stratified according to the site of arterial occlusion: the internal carotid artery or the first or second segment of the middle cerebral artery.

The use of conscious sedation or general anesthesia for endovascular treatment was at the discretion of the neurointerventionist. The site of vessel occlusion was confirmed with the use of digital subtraction angiography. If there was no lesion amenable to thrombectomy, the procedure was terminated. The Solitaire FR retrievable stent (Covidien) was deployed at the site of intracranial-vessel occlusion and then removed under negative-pressure aspiration. Control angiography was performed at the conclusion of the procedure and centrally graded for angiographic revascularization, with the use of the modified Treatment in Cerebral Ischemia classification, on a scale ranging from 0 (no flow) to 3 (normal flow),[16] and any embolization of thrombus into previously uninvolved vascular territories.

STUDY OUTCOMES

The coprimary outcomes were reperfusion (which was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and imaging at 24 hours, which can be negative if hypoperfusion worsens) and early neurologic improvement (which was defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 at 3 days). Secondary outcomes were the score on the modified Rankin scale at 90 days, death due to any cause, and symptomatic intracranial hemorrhage, including any subarachnoid hemorrhage associated with clinical symptoms and symptomatic intracerebral hemorrhage, which was defined as parenchymal hematoma type 2 within 36 hours after treatment combined with an increase on the NIHSS of at least 4 points from baseline.[17] Further details are provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

After the release of the results of the MR CLEAN study, recruitment into the trial was suspended on October 31, 2014, and the data and safety monitoring board reviewed data for the 70 enrolled patients. A prespecified Haybittle–Peto stopping boundary was applied to the coprimary outcome in the intention-to-treat population with the use of Holm's step-down procedure,[18] so that one coprimary outcome was tested at a z value of more than 3.29 and the other at a z value of more than 3. The data and safety monitoring board stopped the trial for efficacy after this analysis.

For the intention-to-treat analysis of the coprimary outcome, we compared the median percentage reperfusion between the endovascular-therapy group and the alteplase-only group after adjustment for baseline arterial occlusion strata using the van Elteren test, a stratified version of the Wilcoxon rank-sum test. We used logistic regression to compare the between-group difference in the proportion of patients with early neurologic recovery, as indicated by a reduction of 8 or more points on the NIHSS or a score of 0 or 1 at 3 days, after adjustment for age and baseline NIHSS score.

Although results are reported with and without adjustment for baseline covariates, the analysis with adjustment was prespecified as the primary analysis. The results are also reported for the target group who underwent endovascular thrombectomy according to the protocol, as compared with the alteplase-only group, to adjust for effects such as recanalization before cerebral angiography was performed and any off-protocol interventions.

As prespecified in the protocol, the initial analysis of the secondary outcome for the score on the modified Rankin scale was designed to be an assumption-free ordinal analysis[19,20] that uses the Wilcoxon–Mann–Whitney generalized odds ratio across the full range of the modified Rankin scale (from 0 to 6). Then, we used a logistic-regression model to compare the proportions of patients with scores of 0 or 1 (defined as an excellent outcome) and those with scores of 0 to 2 (defined as a functionally independent outcome) in the two study groups after adjustment for age and baseline NIHSS score.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)
Age — yr	70.2±11.8	68.6±12.3
Male sex — no. (%)	17 (49)	17 (49)
Median NIHSS score (IQR)†	13 (9–19)	17 (13–20)
Clinical history — no. (%)		
Atrial fibrillation	11 (31)	12 (34)
Hypertension	23 (66)	21 (60)
Diabetes	8 (23)	2 (6)
Smoking	15 (43)	12 (34)
Serum glucose — mmol/liter	7.6±3.6	7.1±2.5
Cause of stroke — no. (%)		
Cardioembolic occlusion	14 (40)	23 (66)
Large-artery occlusion	13 (37)	7 (20)
Undetermined or other	8 (23)	5 (14)
Median time from stroke onset to hospital arrival (IQR) — min	80 (56–115)	78 (54–112)
Median time from stroke onset to initiation of alteplase (IQR) — min	145 (105–180)	127 (93–162)
Site of vessel occlusion — no. (%)		
Internal carotid artery	11 (31)	11 (31)
Middle cerebral artery		
First segment	18 (51)	20 (57)
Second segment	6 (17)	4 (11)
Ischemic core volume at initial imaging — ml‡		
Mean	19.6±17.4	18.9±18.5
Median (IQR)	18 (4–29)	12 (4–32)
Perfusion-lesion volume at initial imaging — ml§		
Mean	116±48	105±39
Median (IQR)	115 (72–158)	106 (76–137)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. IQR denotes interquartile range.

† Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal) to 42 (death), with lower scores indicating less severe stroke.

‡ Irreversibly injured brain (ischemic core) was defined as cerebral blood flow of less than 30% of that in normal tissue.

§ To identify brain tissue at risk for infarction, a perfusion lesion was defined as one with a time to maximum (Tmax) delay of more than 6 seconds on computed tomographic perfusion imaging.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From August 2012 through October 2014, a total of 70 patients underwent randomization (35 to the endovascular-therapy group and 35 to the alteplase-only group) at 10 study centers (9 in Australia and 1 in New Zealand) (Fig. S1 in the Supplementary Appendix). Baseline characteristics of the patients are provided in Table 1, and procedural characteristics in Table 2.

Approximately 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria (Fig. S2 in the Supplementary Appendix). The majority of the thrombus had been lysed before angiography in 4 of 35 patients (11%) in the endovascular-therapy group. Four other patients in the endovascular-therapy group did not undergo thrombectomy because they had either major clinical deterioration or major clinical improvement, stenting of the extracranial internal carotid artery to obtain access achieved a flow with a rating of 2b on the modified Treatment in Cerebral Ischemia classification without requiring thrombectomy, or the procedure was terminated before deployment of the Solitaire FR stent retriever owing to vessel perforation caused by microcatheter manipulation.

EFFICACY

Patients in the endovascular-therapy group had significant improvements in both coprimary end points, as compared with the alteplase-only group (Table 3). Endovascular therapy resulted in increased reperfusion at 24 hours ($P<0.001$) (Fig. 1A) and a probability of reperfusion of more than 90% without symptomatic intracerebral hemorrhage, as compared with the alteplase-only group (89% vs. 34%, $P<0.001$). The improvement in reperfusion remained highly significant in a sensitivity analysis in which 100% reperfusion was imputed for the three patients in the alteplase-

only group who had missing data owing to poor clinical status.

Endovascular therapy led to greater early neurologic recovery at 3 days (P=0.002) (Fig. 1B) and improved functional outcome in an ordinal analysis of the score on the modified Rankin scale at 90 days (generalized odds ratio, 2.0; 95% confidence interval [CI], 1.2 to 3.8; P=0.006) (Fig. 2). We determined that 2.8 patients would need to be treated with endovascular therapy to achieve improvement of at least 1 point on the functional score, as compared with the use of alteplase alone. Patients in the endovascular-therapy group were also more likely to be independent (functional score, 0 to 2) at day 90 (71% vs. 40%, P=0.01); we determined that 3.2 patients would need to be treated to achieve an independent outcome, as compared with alteplase alone. The median number of days spent at home (as compared with in the hospital or other inpatient facility) in the first 90 days after stroke[22] was 64 days greater in the endovascular-therapy group than in the alteplase-only group (P=0.001).

Consistent results were seen across the range of tertiary clinical and imaging end points (Table 3, and Table S3 in the Supplementary Appendix) and the target-group analysis (Table S5 in the Supplementary Appendix). Patients with reperfusion of 90% or more in the affected vascular territory, as compared with those with reperfusion of less than 90%, had improved functional outcome on the ordinal modified Rankin scale at 90 days (generalized odds ratio, 4.5; 95% CI, 2.2 to 9.0; P<0.001) and had increased independence (score, 0 to 2; 72% vs. 30%; P<0.001) and an excellent outcome (score of 0 or 1, 58% vs. 11%; P<0.001).

Table 2. Characteristics of Endovascular Procedures.*

Characteristic	Value
Median time from stroke onset to groin puncture (IQR) — min	210 (166–251)
Median time from hospital arrival to groin puncture (IQR) — min	113 (83–159)
Median time from initial imaging to groin puncture (IQR) — min	93 (71–138)
Median time from initiation of alteplase to groin puncture (IQR) — min	74 (54–97)
Median time from groin puncture to mTICI 2b or 3 or completion of procedure (IQR) — min	43 (24–53)
Median time from stroke onset to mTICI 2b or 3 or completion of procedure (IQR) — min	248 (204–277)
Proportion of patients receiving general anesthesia — no./total no. (%)	12/33 (36)
Final score on mTICI — no./total no. (%)†	
3	14/29 (48)
2b	11/29 (38)
2a	2/29 (7)
1	1/29 (3)
0	1/29 (3)

* The abbreviation mTICI denotes modified Treatment in Cerebral Ischemia classification, with scores ranging from 0 (no flow) to 3 (normal flow). None of the patients who had angiographic reperfusion at the end of the procedure had reocclusion on imaging at 24 hours. Further details are provided in Table S2 in the Supplementary Appendix.

† The final score was measured in the 29 patients who had an initial occlusion on angiography.

SAFETY

Symptomatic intracerebral hemorrhage occurred in two patients in the alteplase-only group (both with fatal results) and in none of the patients in the endovascular-therapy group. However, a large parenchymal hematoma developed in two patients in the endovascular-therapy group without causing major clinical deterioration; in one patient, the bleeding was caused by perforation by a wire during angiography and before deployment of the Solitaire FR stent retriever. Both patients survived, with scores of 3 and 4 on the modified Rankin scale at day 90. Embolization into a different vascular territory occurred in 2 of 35 patients (6%) in the endovascular-therapy group but did not cause clinical symptoms. There was no significant difference in mortality between the two groups, although two of the three patients in the endovascular-therapy group who died had a deterioration in their condition during the initial alteplase infusion before angiography because of a second cerebral embolism. The other adverse procedural event was a groin hematoma requiring transfusion in the endovascular-therapy group. Details regarding adverse events are provided in Table S4 in the Supplementary Appendix.

DISCUSSION

In patients with acute ischemic stroke with major vessel occlusion and salvageable tissue on CT perfusion imaging, early mechanical thrombectomy with the Solitaire FR stent retriever after the intravenous administration of alteplase was associated with faster and more complete reperfusion than the use of alteplase alone. The increase in reperfusion led to a reduction in infarct growth

Table 3. Study Outcomes.*

Outcome	Alteplase-Only Group (N=35)	Endovascular-Therapy Group (N=35)	Effect Size (95% CI)†			
			Adjusted	P Value	Unadjusted	P Value
Primary outcomes						
Median reperfusion at 24 hr (IQR) — (%)‡	37 (−0.5 to 96)	100 (100 to 100)	4.7 (2.5 to 9.0)	<0.001	4.9 (2.5 to 9.5)	<0.001
Early neurologic improvement — no. (%)§	13 (37)	28 (80)	6.0 (2.0 to 18.0)	0.002	6.8 (2.3 to 20)	<0.001
Secondary outcomes						
Score on the modified Rankin scale at 90 days¶						
Median score (IQR) on ordinal analysis	3 (1 to 5)	1 (0 to 3)	2.0	0.02	2.1 (1.2 to 3.8)	0.006
Independent outcome — no. (%)	14 (40)	25 (71)	4.2 (1.4 to 12)	0.01	3.8 (1.4 to 10.0)	0.009
Excellent outcome — no. (%)	10 (29)	18 (51)	2.4 (0.87 to 6.6)	0.09	2.6 (1.0 to 7.1)	0.05
Safety — no. (%)						
Death	7 (20)	3 (9)	0.45 (0.1 to 2.1)	0.31	0.38 (0.1 to 1.6)	0.18
Symptomatic intracerebral hemorrhage‖	2 (6)	0	NA	NA	−6 (−13 to 2)**	0.49
Parenchymal hematoma	3 (9)	4 (11)	NA	NA	3 (−11 to 17)**	0.99
Tertiary outcomes††						
Reperfusion of >90% at 24 hr without symptomatic intracerebral hemorrhage — no. (%)	12 (34)	31 (89)	27.0 (5.5 to 135.0)	<0.001	15.0 (4.0 to 52.0)	<0.001
Recanalization at 24 hr — no. (%)‡‡	15 (43)	33 (94)	29.0 (5.4 to 155.0)	<0.001	22.0 (4.5 to 106.0)	<0.001
Median infarct growth at 24 hr (IQR) — ml§§	35.3 (6.3 to 73.4)	10.9 (0 to 23.6)	−0.44 (−0.76 to −0.13)‖‖	0.007	NA	NA
Median home time (IQR) — days¶¶	15 (0 to 69)	73 (47 to 86)	64 (28 to 90)‖‖	0.001	58 (17 to 90)‖‖	0.006

* NA denotes not applicable.

† Values are odds ratios unless otherwise indicated. Odds ratios or median differences are for the endovascular-therapy group as compared with the alteplase-only group.

‡ Reperfusion was defined as the percentage reduction in the perfusion-lesion volume between initial imaging and 24-hour imaging. This value can be negative if hypoperfusion becomes more severe over time. This analysis was adjusted for the site of vessel occlusion at baseline. The effect size in this category is the Wilcoxon–Mann–Whitney generalized odds ratio.

§ Early neurologic improvement was defined as a reduction of 8 points or more on the National Institutes of Health Stroke Scale (NIHSS) or a score of 0 or 1 at 3 days. This analysis was adjusted for the NIHSS score and age at baseline.

¶ The initial analysis of the modified Rankin scale was an ordinal analysis that used the full range of the scale from 0 (normal function) to 6 (death) and is expressed as a Wilcoxon–Mann–Whitney generalized odds ratio. The analysis was adjusted for the baseline NIHSS score (≤15 vs. >15) and age (≤70 years vs. >70 years) with the use of a permutation method to accommodate small stratum size. This method does not produce confidence intervals. In addition, scores on the modified Rankin scale were analyzed for an outcome with functional independence (score of 0 to 2) or an excellent outcome (score of 0 or 1), adjusted for the full range of ages and baseline score on the NIHSS.

‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.

** The effect size in this category is a risk difference, as measured in percentage points for symptomatic intracerebral hemorrhage and parenchymal hematoma.

†† A more detailed list of tertiary outcomes is provided in Table S3 in the Supplementary Appendix.

‡‡ Recanalization was defined as a Thrombolysis in Myocardial Infarction score of 2 or 3 (partial or complete restoration of flow at the site of arterial occlusion).[21] This analysis was adjusted for the site of vessel occlusion at baseline.

§§ Infarct growth was defined as the increase in the ischemic core volume from baseline to 24 hours and was adjusted for the ischemic core volume at baseline.

¶¶ Home time (the number of days spent at home during the first 90 days after the diagnosis of stroke) was adjusted for the NIHSS score and age at baseline.

‖‖ The effect size in this category is the median difference in infarct growth (as measured in milliliters and transformed by an exponent of 0.2 owing to a non-normal distribution) and the median difference in days for home time, as calculated by median regression.

and substantial clinical benefit in early neurologic recovery and functional outcome at 3 months. This reduction in infarct growth is consistent with salvage of ischemic penumbra as the mechanism of underlying clinical benefit.[23]

The magnitude of the clinical benefit of en-

dovascular thrombectomy in our study was larger than that in previous trials, despite similar clinical severities and demographic characteristics. The results of this trial were unequivocal, despite the small sample size. Key differences between our study and the previous trials include the use of CT perfusion imaging to select patients with the greatest potential to benefit from endovascular therapy, shorter time to the onset of treatment, and improved rates of angiographic revascularization.

A unique feature of our study was the use of standardized, universal CT perfusion-imaging selection to exclude patients with large ischemic cores and without evidence of clinically significant salvageable ischemic brain. Such patients have a low probability of a good outcome and have a higher risk of symptomatic hemorrhage and malignant edema.[15,24] In the time window of less than 4.5 hours, patients with large ischemic cores comprise 10 to 15% of an unselected population,[24] a rate that was generally consistent with the estimate of 25% of patients (95% CI, 11 to 45) who were excluded from our study on the basis of perfusion-imaging criteria. Such patients may not only undergo futile reperfusion but also have a reduced treatment effect if reperfusion leads to hemorrhage or malignant edema. This factor may be particularly relevant if the intervention has a higher reperfusion rate than that in controls, which was shown in our study to be applicable to endovascular therapy. CT perfusion imaging was also performed in about 65% of patients in the MR CLEAN trial (Majoie C: personal communication). Such imaging was not required according to the protocol for the MR CLEAN trial but may have influenced patient selection. Hence, positive results in the MR CLEAN trial may not be entirely attributable to imaging selection on the basis of vessel occlusion alone.

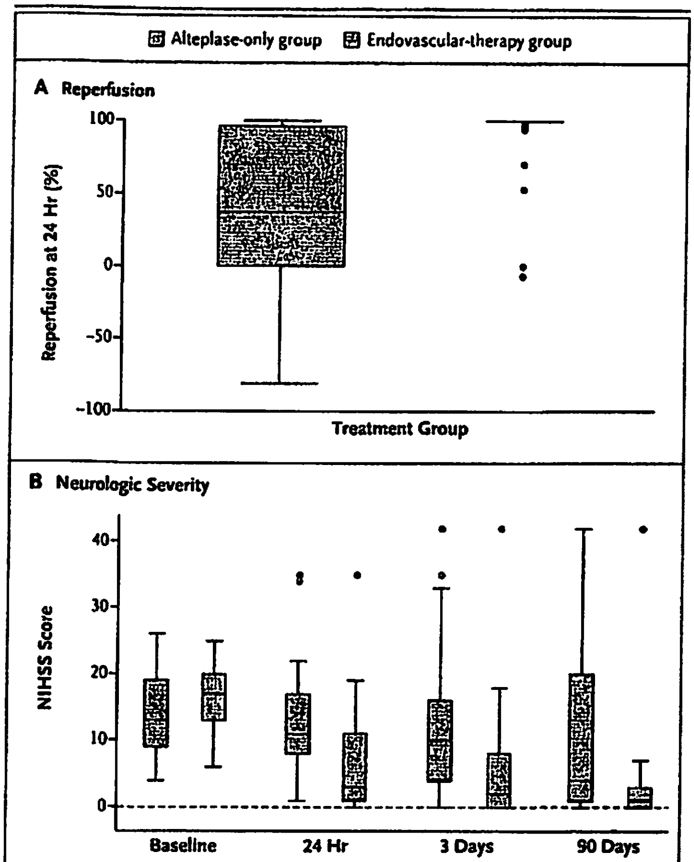

Figure 1. Reperfusion and Functional Scores.

Panel A shows box plots for the rate of reperfusion at 24 hours (the coprimary end point) among patients receiving intravenous alteplase plus endovascular therapy (endovascular-therapy group) and those receiving alteplase only (100% vs. 37%, P<0.001). The horizontal line within the box plot for the alteplase-only group represents the median, the top and bottom of each box indicate the interquartile range, I bars indicate 1.5 times the interquartile range, and the circles indicate outliers. For the endovascular-therapy group, the median was 100%, with six outliers. Panel B shows box plots for the changes in the distribution of scores on the National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 hours, 3 days, and 90 days. NIHSS is a standardized neurologic examination and ranges from 0 (normal) to 42 (death), with lower scores indicating less severe stroke. There was an early and sustained reduction in NIHSS scores in the endovascular-therapy group, as compared with the alteplase-only group.

The interval between the initiation of alteplase and randomization was 30 minutes in our study, as compared with 100 minutes in the MR CLEAN trial, because of our approach of identifying patients with the greatest potential to benefit from reperfusion and then maximizing early reperfusion with the use of combined alteplase and endovascular therapy, rather than waiting to assess clinical response to alteplase. As a result, the time from stroke onset to the initiation of the endovascular procedure was a median of 50 minutes shorter than the similar interval in the MR CLEAN trial, which may also have contributed to the substantially higher proportion of patients with independent functional outcomes observed in our study. Only 11% of the patients in our study had no retrievable thrombus on initial angiography, which is consistent with results that have been reported previously[25] and mitigates any concern regarding unnecessary angiography. As endovascular therapy becomes

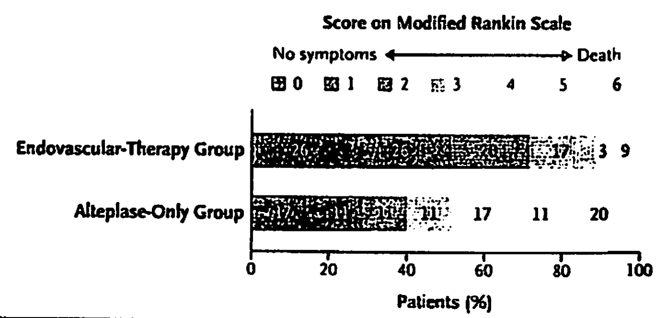

Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Shown are the percentages of patients in the endovascular-therapy group and the alteplase-only group with scores from 0 to 6 on the modified Rankin scale as follows: 0, no symptoms; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death. In the endovascular group, no patients had a score of 5.

standard care, there is further potential to streamline the "door-to-puncture" process and perhaps achieve even greater clinical benefits.

The rate of successful revascularization immediately after the procedure (86% of patients had a restoration of flow to >50% of the stroke-affected territory) was higher in our study than in previous randomized trials but is consistent with registry studies in which the Solitaire FR stent retriever was used.[5] This finding probably relates to the use of earlier-generation devices and techniques in the IMS-3 and the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials. The reperfusion rate in our study was also higher than the 58% reported in MR CLEAN, in which stent retrievers were used in 81.5% of patients. There is some evidence that the success of recanalization is increased in patients with good collateral flow,[26] which correlates strongly with the presence of a "mismatch" pattern on perfusion imaging between a small, irreversibly injured ischemic core and a larger perfusion lesion indicating the presence of salvageable ischemic penumbra.[27] The imaging selection of patients may therefore have chosen patients with a better chance of recanalization.

Our study, which was conducted at multiple centers with varying levels of imaging expertise, shows the practicality and generalizability of fully automated image processing. The time that is required to acquire, process, and interpret images is largely a function of computer-network speed and processing power, and should be less than 15 minutes.[12] Analysis of the CT perfusion images occurred in parallel with administration of alteplase so that there was no treatment delay.[28]

Strengths of our study include the selection of patients who were most likely to benefit from reperfusion, earlier intervention, and a standardized stent-retriever intervention with more complete revascularization. Also, the routine assessment of reperfusion at 24 hours has the advantage of being quantitative, blinded, and objective because of the automated software that was used. The 24-hour interval provides assurance that reocclusion after initial successful recanalization is uncommon in such patients. Previous studies have been restricted to assessing angiographic reperfusion rates in only the endovascular group or, in some cases, recanalization at 24 hours in a subgroup of patients.[2]

Limitations of the study include the inability to perform subgroup analyses, given the small number of patients. Such analyses will require individual patient meta-analysis of multiple trials. We cannot rule out the possibility that some of the patients who were excluded from the trial on the basis of a large ischemic core or absence of significant salvageable ischemic brain tissue might have benefited from endovascular therapy. Purely volume-based criteria do not account for the location of the core, which is also relevant to the clinical outcome.[29] The early termination of the trial does create potential for overestimation of the effect size. However, the investigators believed that the new information from the MR CLEAN trial ethically mandated review by the independent data and safety monitoring board. The details of the statistical stopping rule were highly conservative and were agreed on between investigators and the data and safety monitoring board in advance of accessing the data.

In conclusion, we found that patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging had improved reperfusion, early neurologic recovery, and functional outcome if endovascular thrombectomy with the Solitaire FR stent retriever was performed without delay after the

initiation of intravenous alteplase. Further studies will be needed to clarify remaining uncertainties regarding the benefit in patients with more distal occlusions, later time windows, and the influence of the type of device that is used and variability in the endovascular technique.

Supported by grants from the Australian National Health and Medical Research Council of Australia (1043242 and 1035688), Royal Australasian College of Physicians, Royal Melbourne Hospital Foundation, and the National Heart Foundation of Australia; and by infrastructure funding from the state government of Victoria. The Solitaire FR device and trial infrastructure were provided under an unrestricted grant from Covidien.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Gregory Albers, Roland Bammer, and staff members at the Stanford University Stroke Center for providing a research version of the RAPID software; Simon McBride, Christopher Stanbridge, and Karen Harrap of the Commonwealth Scientific and Industrial Research Organization for creating the electronic-case-record and Internet randomization; Gagan Sharma and Simon Salinas for imaging-data management; and Elise Cowley and Rachael McCoy of Neuroscience Trials Australia for study management.

APPENDIX

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ORIGINAL ARTICLE

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

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ABSTRACT

BACKGROUND

Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

METHODS

We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin scale (with scores ranging from 0 [no symptoms] to 6 [death]).

RESULTS

The study was stopped early because of efficacy. At 39 centers, 196 patients underwent randomization (98 patients in each group). In the intervention group, the median time from qualifying imaging to groin puncture was 57 minutes, and the rate of substantial reperfusion at the end of the procedure was 88%. Thrombectomy with the stent retriever plus intravenous t-PA reduced disability at 90 days over the entire range of scores on the modified Rankin scale (P<0.001). The rate of functional independence (modified Rankin scale score, 0 to 2) was higher in the intervention group than in the control group (60% vs. 35%, P<0.001). There were no significant between-group differences in 90-day mortality (9% vs. 12%, P=0.50) or symptomatic intracranial hemorrhage (0% vs. 3%, P=0.12).

CONCLUSIONS

In patients receiving intravenous t-PA for acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, thrombectomy with a stent retriever within 6 hours after onset improved functional outcomes at 90 days. (Funded by Covidien; SWIFT PRIME ClinicalTrials.gov number, NCT01657461.)

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*A complete list of investigators in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 17, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1415061

INTRAVENOUS TISSUE PLASMINOGEN ACTIvator (t-PA) administered within 4.5 hours after the onset of acute ischemic stroke improves outcomes.[1-3] However, intravenous t-PA has multiple constraints, including unresponsiveness of large thrombi to rapid enzymatic digestion, a narrow time window for administration, and the risk of cerebral and systemic hemorrhage. Among patients with occlusions of the intracranial internal carotid artery or the first segment of the middle cerebral artery (or both), intravenous t-PA results in early reperfusion in only 13 to 50%.[4-7]

Neurovascular thrombectomy is a reperfusion strategy that is distinct from pharmacologic fibrinolysis. Endovascular mechanical treatments can remove large, proximal clots rapidly and result in higher rates of reperfusion than intravenous t-PA alone. Three initial trials of endovascular therapies did not show a benefit for thrombectomy over intravenous t-PA or supportive medical care, but they were limited by the use of intraarterial delivery of t-PA or the use of early-generation devices with modest reperfusion efficacy (or both), the failure of two trials to use vessel imaging to confirm the presence of an appropriate target occlusion, and the slow initiation of endovascular intervention.[8-10]

The Solitaire revascularization device (Covidien) is a self-expanding stent used to retrieve thrombi and restore blood flow. In multicenter registries and one randomized trial, this stent retriever, as compared with early-generation mechanical thrombectomy devices, was associated with faster and more frequent reperfusion, reduced intracranial hemorrhage, and improved disability outcome.[11-15]

We performed the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial to establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. This trial was among several contemporaneous trials launched worldwide to test new-generation strategies for mechanical thrombectomy.[16-18] Our trial was conducted in multiple countries and health systems as a registration trial capable of supporting expansion of regulatory labeling. We used a uniform device procedure in the intervention group and tested intracranial neurovascular thrombectomy alone rather than in combination with cervical stenting.

METHODS

TRIAL DESIGN

In this international, multicenter, prospective, randomized, open clinical trial, we compared intravenous t-PA followed by neurovascular thrombectomy with the use of a stent retriever with intravenous t-PA alone in patients with acute ischemic stroke. All the patients had confirmed occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on vessel imaging and an absence of large ischemic-core lesions. Patients were randomly assigned in a 1:1 ratio to one of two treatment groups: intravenous t-PA plus stent retriever (intervention group) or intravenous t-PA alone (control group). Using a minimization algorithm, we balanced the numbers of patients in the two treatment groups with respect to four factors: investigational site, baseline severity according to the National Institutes of Health Stroke Scale (NIHSS) score (≤17 vs. >17, on a scale of 0 to 42, with higher scores indicating greater severity), age (<70 years vs. ≥70 years), and occlusion location (middle cerebral artery vs. internal carotid artery).

Details of the study design have been published previously.[19] The study was conducted and reported with fidelity to the study protocol, available with the full text of this article at NEJM.org. (An overview of the study procedure is provided in Fig. S1 in the Supplementary Appendix, available at NEJM.org.)

The trial was approved by the institutional review board at each site. Enrolled patients provided written informed consent, or at select sites, there was an exception from explicit informed consent in emergency circumstances.

The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor. The first and subsequent drafts of the manuscript were written by the first and second authors, incorporating input from all the authors. The academic authors had unrestricted access to the data, performed the data analysis with the primary and the independent study statisticians, and attest to the integrity of the trial and the completeness and accuracy of the reported data. The trial was monitored by an independent data and safety monitoring board.

PATIENTS AND PARTICIPATING CENTERS

The study was performed at 39 centers in the United States and Europe. All study centers were required to have performed at least 40 mechanical-thrombectomy procedures, including at least 20 procedures with the Solitaire stent retriever, annually. Entry criteria selected patients who had acute ischemic stroke with moderate-to-severe neurologic deficits; had imaging-confirmed occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both; met the imaging eligibility requirements; were receiving or had received intravenous t-PA; and were able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. Qualifying imaging had to be performed at a study hospital; imaging was repeated for patients who were transferred from outside hospitals. Detailed study inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix.

To identify patients with salvageable tissue, at trial launch the entry criteria regarding imaging selection required patients to have a target-mismatch penumbral profile, with a small core of tissue that was likely to be irreversibly injured and a large region of hypoperfused tissue that was likely to be salvageable. Penumbral imaging analysis was performed with the use of RAPID (iSchemaView), an operator-independent image-postprocessing system.[20] After the enrollment of the first 71 patients, these criteria were revised to use a small-to-moderate core-infarct strategy (Table S1 in the Supplementary Appendix) to accommodate study sites with limited perfusion-imaging capability and to ensure accelerated treatment delivery. Study sites with advanced imaging capability were still encouraged to obtain penumbral imaging and to exclude patients who did not meet the target-mismatch profile.

INTERVENTION

In the intervention group, neurovascular thrombectomy was performed with the use of the Solitaire FR (Flow Restoration) or Solitaire 2 device. Concomitant stenting of the cervical internal carotid artery was not permitted, although angioplasty could be performed to permit intracranial access.

A studywide continuous quality-improvement program emphasized the speed and quality of the neurointerventional workflow, including rapid patient transfer to the neuroangiography suite and procedure performance. The study target for the time from qualifying imaging to groin puncture was within 70 minutes.

OUTCOME MEASURES

The primary study-outcome measure was disability at 90 days, as assessed by means of the modified Rankin scale, a global measure of disability on a seven-level scale, with scores ranging from 0 (no symptoms) to 6 (death) (Fig. 1). (Details on the use of this scale are provided in the Supplementary Appendix.)

Secondary clinical efficacy outcomes were the rate of death at 90 days, the rate of functional independence (modified Rankin scale score, ≤2) at 90 days, and the change in the NIHSS score at 27 hours after randomization. The technical efficacy outcomes regarding revascularization were substantial reperfusion, as assessed by means of catheter angiography in the intervention group and defined as a modified Thrombolysis in Ce-

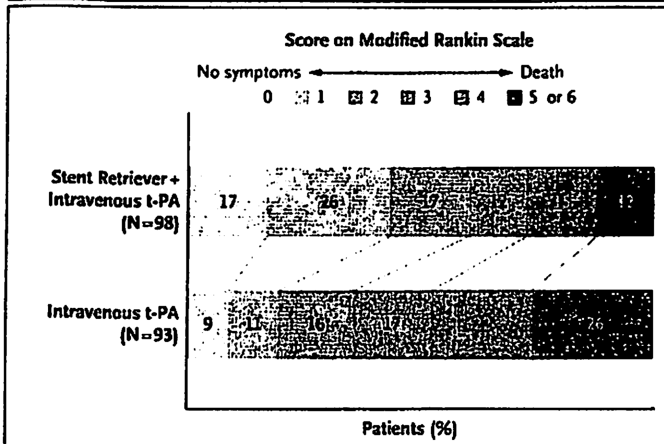

Figure 1. Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.

Shown are the 90-day scores on the modified Rankin scale for the patients in the two treatment groups. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be independent in daily function. Neurovascular thrombectomy with the use of a stent retriever was associated with a significant shift in the distribution of scores toward lesser disability ($P<0.001$ by the Cochran–Mantel–Haenszel test), including an absolute increase of 25 percentage points in the proportion of patients who were functionally independent at 90 days ($P<0.001$). The term t-PA denotes tissue plasminogen activator.

rebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion)[21]; and successful reperfusion at 27 hours in the two study groups, which was defined as reperfusion of 90% or more of the initial perfusion-lesion volume, as assessed by means of perfusion imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) at 27 hours after randomization. Prespecified safety outcomes were all serious adverse events through study completion and symptomatic intracranial hemorrhage at 27 hours after randomization.

CLINICAL AND RADIOLOGIC ASSESSMENT

Clinical assessments were performed at baseline, 27 hours after randomization, 7 to 10 days (or at discharge if earlier), 30 days, and 90 days. Clinical evaluations included the score on the modified Rankin scale for assessing global disability and the NIHSS score for assessing neurologic deficit. Entry and outcome neurovascular images were assessed in a blinded manner by staff at the core imaging laboratories (iSchemaView for penumbral and volumetric imaging and Synarc for parenchymal and angiographic imaging).

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Age — yr	66.3±11.3	65.0±12.5
Male sex — no./total no. (%)	45/96 (47)	54/98 (55)
Race — no./total no. (%)†		
White	83/92 (90)	79/90 (88)
Black	8/92 (9)	10/90 (11)
Asian or other	1/92 (1)	1/90 (1)
Hispanic ethnic group — no. (%)†	7/92 (8)	8/90 (9)
NIHSS score‡		
Median	17	17
Interquartile range	13–19	13–20
Prestroke score of 0 or 1 on modified Rankin scale — no./total no. (%)§	93/94 (99)	96/98 (98)
Medical history — no./total no. (%)		
Hypertension	56/97 (58)	66/98 (67)
Diabetes mellitus	15/97 (15)	12/98 (12)
Current or past tobacco use	39/93 (42)	41/96 (43)
Atrial fibrillation	38/97 (39)	35/98 (36)
Myocardial infarction	11/97 (11)	8/98 (8)
Serum glucose — mg/dl¶	131±47	131±46
Administration of intravenous t-PA at outside hospital — no./total no. (%)	35/94 (37)	31/98 (32)
Interval from symptom onset to start of intravenous t-PA — min		
Median	117	110.5
Interquartile range	80–155	85–156
Parenchymal imaging variable		
ASPECTS value‖		
Median	9	9
Interquartile range	8–10	7–10
Penumbral imaging performed — no./total no. (%)	75/97 (77)	83/98 (85)
Target-mismatch profile — no./total no. (%)**	64/75 (85)	69/83 (83)

Table 1 (Continued.)

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Site of intracranial-artery occlusion — no./total no. (%)		
Internal carotid artery	15/94 (16)	17/93 (18)
Middle cerebral artery		
First segment	72/94 (77)	62/93 (67)
Second segment††	6/94 (6)	13/93 (14)
Process time — min		
Stroke onset to randomization		
Median	188	190.5
Interquartile range	130–268	141–249
Stroke onset to groin puncture		
Median	NA	224
Interquartile range	NA	165–275
Stroke onset to first deployment of stent retriever		
Median	NA	252
Interquartile range	NA	190–300
Arrival in emergency department to groin puncture		
Median	NA	90
Interquartile range	NA	69–120
Qualifying image to groin puncture		
Median	NA	57
Interquartile range	NA	40–80

* Plus–minus values are means ±SD. There were no significant differences between the two groups. One patient in the group that received intravenous tissue plasminogen activator (t-PA) alone requested the deletion of all data. Three additional patients in the group that received intravenous t-PA alone (1 patient who died and 2 who withdrew) are missing some baseline data owing to early study exit, including data on the prestroke modified Rankin Scale score, the hospital site of intravenous t-PA administration, and site of intracranial-artery occlusion for all 3 patients, and data on sex, race, and ethnic group for 1. Data on race and ethnic group were missing for all 13 patients in France owing to national regulations. Data regarding the location of the arterial occlusion were missing for 7 patients because the core laboratory considered that imaging could not be assessed with complete reliability. Two patients were deemed by the core laboratory to not have occlusions in the internal carotid artery or the first or second segment of the middle cerebral artery. A total of 37 patients did not have baseline penumbral imaging performed, after a protocol amendment making penumbral imaging optional. Data regarding additional baseline characteristics are shown in Table S4 in the Supplementary Appendix. NA denotes not applicable.

† Race and ethnic group were self-reported.

‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit.

§ Scores on the modified Rankin scale for the assessment of global disability range from 0 (no symptoms) to 6 (death).

¶ To convert the values for glucose to millimoles per liter, multiply by 0.05551.

‖ The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core.

** The target-mismatch profile was defined as meeting the following criteria as assessed on CT perfusion or diffusion imaging and perfusion MRI: the core infarct lesion measured 50 ml or less, the volume of tissue with a time to maximum delay of more than 10 seconds was 100 ml or less, and the mismatch volume was at least 15 ml and the mismatch ratio was more than 1.8:1.0.

†† These occlusions were classified as first-segment occlusions by the treating site at the time of study entry but as second-segment occlusions by the core imaging laboratory.

STATISTICAL ANALYSIS

For the primary outcome, we analyzed the score on the modified Rankin scale at 90 days using simultaneous success criteria of the overall distribution of the score (shift in disability levels) and the proportion of patients who were functionally independent. Both criteria needed to be met in order for the study to be declared positive. The statistical hypothesis on the scale shift was that the distribution over the entire range of scores (except for scores of 5 or 6, which were collapsed into a single group) among patients in the intervention group would be more favorable than the distribution in the control group, as analyzed by means of the Cochran–Mantel–Haenszel test.

A simultaneous requirement for success was that the difference in the proportion of patients with a score of 0 to 2 nominally meet a prespecified minimum, which varied according to the final sample size at trial discontinuation or completion, with a larger benefit required with a smaller sample size (Table S2 in the Supplementary Appendix). Missing final scores on the modified Rankin scale were handled with the use of the last-observation-carried-forward approach when a score was available from the 30-day visit or the visit at 7 to 10 days. Power and sample size were determined with the use of the dual success criteria, incorporating a group sequential-analysis plan with five interim analyses for efficacy, futility, and safety. (Details are provided in Table S2 in the Supplementary Appendix and in the full statistical analysis plan in the protocol.)

After the preliminary results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial were reported,[16,18] our data and safety monitoring board recommended holding enrollment, and the first interim efficacy analysis was performed slightly early (including 196 rather than 200 patients). In February 2015, the study was halted when the interim efficacy analysis showed that the prespecified stopping-criteria boundary for efficacy had been crossed. A test to determine whether the data across clinical sites could be pooled showed no evidence of heterogeneity of treatment effect ($P=0.73$ by the Breslow–Day test), so pooled study results are presented. All P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From December 2012 through November 2014, 196 patients underwent randomization (98 in each group) at 39 centers in the United States and Europe. Reasons for exclusion are listed in Table S3 in the Supplementary Appendix.

The demographic and clinical characteristics of the two treatment groups at baseline were well balanced (Table 1, and Table S4 in the Supplementary Appendix). Figure S2 in the Supplementary Appendix shows the enrollment and follow-up of patients in the trial.

INTERVENTION

In the intervention group, the time from symptom onset to groin puncture was 224 minutes (interquartile range, 165 to 275), the time from the start of intravenous t-PA to groin puncture was 77 minutes (interquartile range, 50 to 142), and the time from study-qualifying brain imaging to groin puncture was 57 minutes (interquartile range, 40 to 80). In the intervention group, the stent retriever was deployed in 87 patients (89%); the reasons for nondeployment are listed in Table S5 in the Supplementary Appendix. Among these 87 patients, the median time from groin puncture to first deployment of the stent retriever was 24 minutes (interquartile range, 18 to 33). General anesthesia was used in 36 patients (37%) in the intervention group.

PRIMARY OUTCOME

Treatment with thrombectomy with the use of the stent retriever met both of the simultaneous success criteria. Thrombectomy treatment was associated with a favorable shift in the distribution of global disability scores on the modified Rankin scale at 90 days ($P<0.001$ by the Cochran–Mantel–Haenszel test, which was lower than the P value of 0.01 that was specified for early stopping; number needed to treat for one additional patient to have a less-disabled outcome, 2.6). The shift toward better outcomes was consistent in direction across all the score levels of the modified Rankin scale (Fig. 1). The proportion of patients who were functionally independent (modified Rankin scale score, ≤2) at 90 days was

higher in the intervention group than in the control group, with an absolute difference of 25 percentage points, which exceeded the 12-percentage-point boundary that was prespecified for early stopping. Results remained significant in sensitivity analyses that used multiple imputation and worst-case and best-case scenarios to account for missing data (Table S6 in the Supplementary Appendix) and in analyses that were adjusted for imbalances in baseline prognostic features (Table S7 and Fig. S3 in the Supplementary Appendix).

SECONDARY OUTCOMES

Prespecified secondary clinical efficacy outcomes and technical efficacy outcomes regarding revascularization are shown in Table 2; additional prespecified and post hoc outcomes are shown in Tables S10 and S13 in the Supplementary Appendix. The proportion of outcomes indicating functional independence at 90 days was significantly higher in the intervention group than in the control group, with an absolute difference of 25 percentage points (95% confidence interval [CI], 11 to 38) and a risk ratio of 1.70 (95% CI, 1.23 to 2.33; $P<0.001$; number needed to treat for one additional patient to be functionally independent, 4.0). Mortality at 90 days did not differ significantly between the intervention group and the control group (9% and 12%, respectively; $P=0.50$).

In the intervention group, substantial reperfusion (50 to 99%) or complete reperfusion (100%) at the end of the procedure occurred in 73 of the 83 patients (88%) who underwent placement of the stent retriever (Table S9 in the Supplementary Appendix). A total of 4 additional patients who

Table 2. Primary and Secondary Outcomes.*

Outcome	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
Primary outcome: score on modified Rankin scale at 90 days†				<0.001
No. of patients with data	93	98		
Median score	3	2		
Interquartile range	2–5	1–4		
Secondary outcomes				
Clinical efficacy outcome				
Functional independence at 90 days — no./total no. (%)‡	33/93 (35)	59/98 (60)	1.70 (1.23–2.33)	<0.001
Change in NIHSS score at 27 hr				
No. of patients with data	92	97		
Mean change	−3.9±6.2	−8.5±7.1		<0.001
Death at 90 days — no./total no. (%)§	12/97 (12)	9/98 (9)	0.74 (0.33–1.68)	0.50
Revascularization outcome¶				
Substantial reperfusion immediately after thrombectomy — no./total no. (%)	NA	73/83 (88)	NA	NA
Successful reperfusion at 27 hr — no./total no. (%)	21/52 (40)	53/64 (83)	2.05 (1.45–2.91)	<0.001

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not applicable.
† Shown are the results of the prespecified Cochran–Mantel–Haenszel test for the shift in disability score. Similar results were found in the analysis of the common odds ratio (odds ratio, 2.63; 95% CI, 1.57 to 4.40; $P<0.001$).
‡ Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.
§ One patient in the group that received intravenous t-PA alone requested the deletion of all data, including vital status.
¶ Substantial reperfusion was defined as reperfusion of at least 50% and a modified Thrombolysis in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion). Successful reperfusion was defined as reperfusion of at least 90%, as assessed with the use of perfusion CT or MRI. Data on successful reperfusion were not obtained for all the patients after the adoption of the protocol amendment making penumbral imaging optional.

underwent the intervention did not have a final angiogram that could be assessed. Successful reperfusion (≥90%) at 27 hours, assessed by means of perfusion CT or MRI, was more frequent in the intervention group than in the control group (53 of 64 patients [83%] vs. 21 of 52 [40%], P<0.001).

SAFETY

The rates of serious adverse events (36% in the intervention group and 31% in the control group, P=0.54) and symptomatic intracranial hemorrhage (0% and 3%, respectively; P=0.12) did not differ significantly between the treatment groups (Table 3, and Table S11 in the Supplementary Appendix). There was no significant between-group difference in the rate of all intracranial hemorrhage subtypes that were assessed radiologically, but there were numerically more subarachnoid hemorrhages in the intervention group than in the control group (four patients and one patient, respectively; P=0.37). No serious adverse events and seven nonserious adverse events were adjudicated to be device-related (Table S12 in the Supplementary Appendix).

SUBGROUP ANALYSES

Within the constraints of the study sample size, no evidence of heterogeneity of treatment effect was detected in any of the eight prespecified subgroups (Fig. 2, and Fig. S4 in the Supplementary Appendix). The benefit of thrombectomy with the stent retriever plus intravenous t-PA over intravenous t-PA alone was also observed in the prespecified subgroup of patients who received intravenous t-PA within 3 hours after symptom onset (P<0.001) (Table S8 in the Supplementary Appendix).

DISCUSSION

Our study showed that in patients with acute ischemic stroke with confirmed large-vessel occlusions of the anterior circulation who were treated with intravenous t-PA, treatment with the stent retriever within 6 hours after symptom onset improved functional outcomes at 90 days. For every 2.6 patients who were treated, 1 additional patient had an improved disability outcome; for every 4.0 patients who were treated, 1 additional patient was functionally independent at 90-day follow-up.

These findings confirm and extend those of recent trials.[16-18] Our trial emphasized speedy endovascular therapy in patients selected by means of imaging, similar to the protocol used in the ESCAPE trial,[18] and achieved onset-to-reperfusion

Table 3. Safety Outcomes.*

Outcome	Intravenous t-PA Alone (N=97)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	P Value
	no. of patients (%)			
Primary safety outcomes				
Any serious adverse event at 90 days†	30 (31)	35 (36)	1.15 (0.78–1.72)	0.54
Symptomatic intracranial hemorrhage at 27 hr	3 (3)	0	0.00 (NA)	0.12
Additional safety outcomes at 27 hr				
Parenchymal hematoma	7 (7)	5 (5)	0.71 (0.23–2.15)	0.57
Type 1	3 (3)	4 (4)	1.32 (0.30–5.74)	1.00
Type 2	4 (4)	1 (1)	0.25 (0.03–2.17)	0.21
Subarachnoid hemorrhage	1 (1)	4 (4)	3.96 (0.45–34.79)	0.37

* NA denotes not applicable.
† A serious adverse event was an adverse event that led to death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or fetal distress, fetal death or a congenital anomaly or birth defect. Serious adverse events that are classified according to organ system are shown in Table S11 in the Supplementary Appendix. None of the serious adverse events were adjudicated by the clinical-events committee to be device-related. Nonserious adverse events that were deemed to be device-related are shown in Table S12 in the Supplementary Appendix.

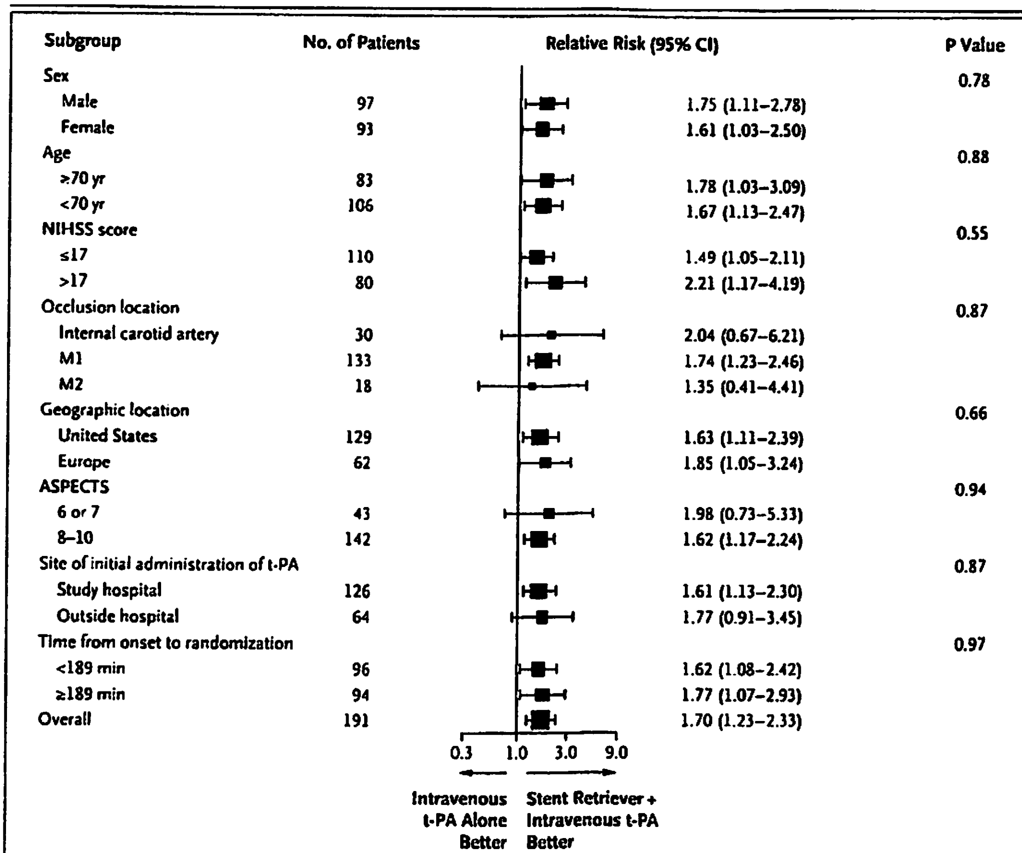

Figure 2. Analysis of Functional Independence at 90 Days in Prespecified Subgroups.

Functional independence was defined as a score on the modified Rankin scale of 0, 1, or 2. P values were based on the Breslow–Day test for homogeneous odds ratios across subgroups. Squares indicate point estimates for treatment effects, and the size of the square is proportional to the precision of the estimate. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The threshold of 17 was the threshold used in stratifying randomization. The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core; a score of 6 or 7 indicates moderate infarct core, and a score of 8 or higher small infarct core. For the time from stroke onset to randomization, the median value was prespecified as the cutoff point for analysis and was found to be 189 minutes. M1 denotes first segment of the middle cerebral artery, and M2 second segment of middle cerebral artery.

times that were faster than those in MR CLEAN[16] and in studies of early-generation interventions.[8-10] The median time from arrival in the emergency department to groin puncture of 90 minutes was faster than the 120-minute target that is recommended in current multisociety guidelines.[22] In our trial, study sites were provided with a prespecified efficiency target of performing groin puncture within 70 minutes after qualifying imaging, and continuous central review encouraged rapid workflow. For patients with intravenous t-PA that was initiated at study centers, groin puncture and stent-retriever deployment could take place while t-PA was infusing.

Several aspects of the treatment and treatment response were distinctive in our study. The rate of substantial or complete reperfusion (88%) among patients undergoing intracranial intervention was higher in this trial than in previous trials. The high reperfusion rate is probably due in part to the more homogeneous patient population (more occlusions in the first segment of the middle cerebral artery and fewer intracranial or cervical occlusions of the internal carotid artery) and the more homogeneous intervention (an ef-

fective stent retriever and no other device classes and no intraarterial fibrinolytic agent) in this trial than in earlier trials. The frequency of functional independence in the intervention group was high in our trial (60%) and was greater than that observed in MR CLEAN (33%) and similar to that observed in the ESCAPE trial (53%) and the Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND IA) trial (71%).[17] The high frequency of this outcome probably reflects the earlier start of the intervention,[23-26] the exclusion of patients with large core infarcts on the basis of imaging,[27,28] and the greater reperfusion rate in our trial, as compared with the other trials.

No significant differences in treatment effect were detected across all the prespecified subgroups, including such factors as age, sex, degree of neurologic deficit, site of occlusion, and size of infarct core on qualifying imaging, although the moderate sample size limited the power of this analysis. We also performed a prespecified analysis comparing patients who received intravenous t-PA at an outside hospital and were transferred to a study center for thrombectomy with those who received both the intravenous t-PA and the endovascular intervention at the study center. One third of the patients were treated with intravenous t-PA at an outside hospital. These patients had less favorable outcomes overall; however, their relative benefit from endovascular therapy did not differ significantly from that observed in patients who received intravenous t-PA at the study site (Fig. 2, and Fig. S4 in the Supplementary Appendix).

The rates of serious adverse events did not differ significantly between the study groups overall or within major organ categories, and no device-specific serious adverse events were observed. The most common nonserious device-specific adverse event was transient, intraprocedural vasospasm without clinical sequelae. Rates of symptomatic hemorrhage were low and did not differ significantly between the two treatment groups. Subarachnoid hemorrhage and intracerebral hematomas as assessed radiologically were also uncommon.

Our study has several limitations. First, we studied a homogeneous cohort of patients treated with intravenous t-PA; additional trials are needed to delineate the effects of stent-retriever therapy in other populations of patients with acute ischemic stroke, including those who are ineligible for intravenous t-PA, those who present more than 6 hours after symptom onset (including those who awaken after having had a stroke), and those with occlusions in the second segment of the middle cerebral artery or the posterior circulation. Second, study conduct included a continuous quality-improvement program to improve endovascular workflow efficiency at the participating sites. Implementation of similar quality-improvement programs in routine care settings,[29] as has been done on a broad scale for intravenous t-PA,[30] would be required to ensure similar stent-retriever outcomes in regular practice. Finally, all the enrolling sites were tertiary care centers with established stroke-intervention programs staffed by experienced neurointerventionalists. These results may not be generalizable to clinical sites without requisite neurointerventional expertise.

In conclusion, we found that in patients with acute ischemic stroke due to large-vessel occlusion who had small or moderate ischemic cores, emergency neurovascular thrombectomy with the stent retriever was safe and effective in achieving reperfusion and substantially reduced the degree of disability and increased the proportion of patients with functional independence 3 months after stroke.

Supported by Covidien.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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kum der Goethe–Universität, Frankfurt — all in Germany; the Department of Neurosurgery (E.I.L., A.H.S.) and Toshiba Stroke and Vascular Research Center (A.H.S.), State University of New York at Buffalo, Buffalo; Saint Luke's Mid America Heart Institute and University of Missouri–Kansas City School of Medicine, Kansas City (D.J.C.); the Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh (T.G.J., V.K.R.); the Department of Neurology, Inselspital, University of Bern, Bern, Switzerland (H.P.M.); the Marcus Stroke and Neuroscience Center, Grady Memorial Hospital, Department of Neurology, Emory University School of Medicine, Atlanta (R.G.N.); the Department of Neurology and Neurosurgery, University of Miami Miller School of Medicine–Jackson Memorial Hospital, Miami (D.R.Y.); the Department of Radiology (B.W.B.) and Division of Neurology (T.G.D.), Erlanger Hospital at the University of Tennessee, Chattanooga; and the Department of Neurosurgery, Rush University Medical Center, Chicago (D.K.L.).

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